

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

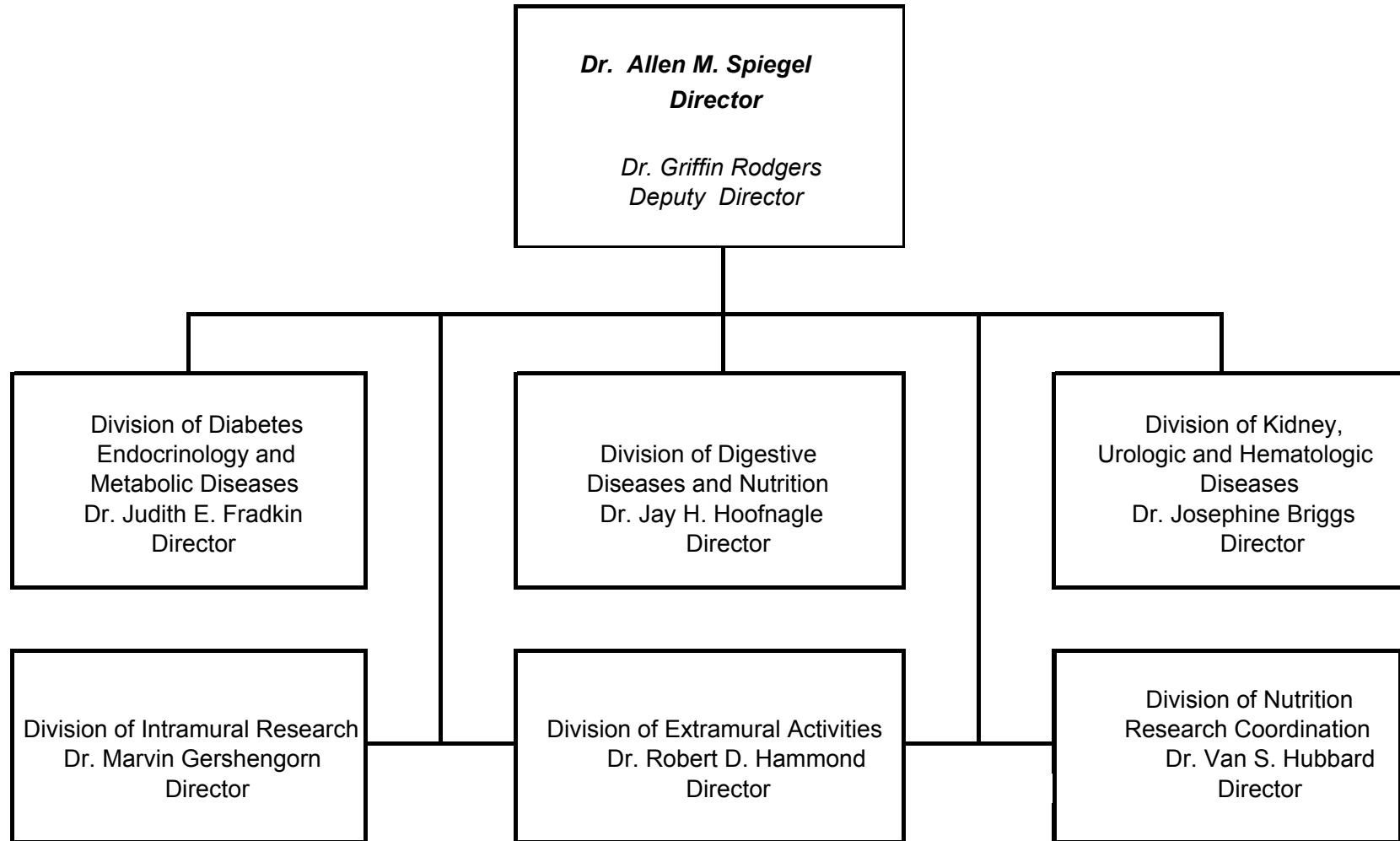
National Institute of Diabetes and Digestive and Kidney Diseases

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NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

For carrying out Section 301 and Title IV of the Public Health Service Act with respect to diabetes and digestive and kidney diseases, [1,466,833,000] *\$1,578,913,000*.

[Departments of Labor, Health and Human Services, Education, and Related Agencies

Appropriation Act, for Fiscal Year, 2002, (P.L. 107-116)]

National Institutes of Health

National Institute of Diabetes and Digestive and Kidney Diseases

Amounts Available for Obligation 1/ , 2/

Source of Funding	FY 2001 Actual	FY 2002 Estimate	FY 2003 Estimate
Appropriation	\$1,373,385,000	\$1,466,833,000	\$1,574,268,000
Enacted Rescission	(429,000)	(453,000)	---
Subtotal, Adjusted Appropriation	1,372,956,000	1,466,380,000	1,574,268,000
Comparable adjustment for legislative proposal for accrued retirement costs	4,096,000	4,435,000	4,645,000
Real transfer to: Other HHS Agencies through Secretary's one-percent transfer authority	(247,000)	---	---
Real transfer to HHS for the Office of Human Research Protection	(272,000)	---	---
Real transfer from: State Children's Health Insurance Program in the Health Care Financing Administration for Type 1 Diabetes Research	27,000,000	---	---
Comparative transfer from: Office of the Director for the Academic Research Enhancement Award program	1,133,000	0	
National Cancer Institute for research activities	---	---	30,379,000
Comparative transfer to: National Institute of Biomedical Imaging and Bioengineering	(772,000)	(0)	0
Subtotal, adjusted budget authority	1,403,894,000	1,470,815,000	1,609,292,000
Unobligated balance, lapsing	(253,000)	---	---
Total obligations	1,403,641,000	1,470,815,000	1,609,292,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:

FY 2001 - \$10,206,000; FY 2002 - \$10,206,000; FY 2003 - \$10,206,000

Excludes \$900,000 in FY 2001 and \$930,000 in FY 2002 for royalties.

2/ Excludes the following amounts for reimbursable activities carried out by this account:

Excludes \$11,000 for accrued cost reimbursements in FY 2002 and \$11,000 in FY 2003.

Justification

National Institute of Diabetes and Digestive and Kidney Diseases

Authorizing Legislation: Section 301 of the Public Health Service Act, as amended.
Reauthorizing legislation will be submitted.

Budget Authority:

	2001 Actual	2002 Appropriation	2002 Current Estimate	2003 Estimate	Increase or Decrease
Current Law BA	\$1,399,798,000	\$1,466,833,000	\$1,466,380,000	\$1,604,647,000	\$138,267,000
Accrued Costs	4,096,000	4,435,000	4,435,000	4,645,000	210,000
Proposed Law BA	1,403,894,000	1,471,268,000	1,470,815,000	1,609,292,000	138,477,000
FTE	627	645	645	642	-3

This document provides justification for the Fiscal Year 2003 activities of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2003 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

The President's appropriations request of \$1,609,292,000 for this account includes current law adjusted by assuming Congressional action on the proposed Managerial Flexibility Act of 2001.

Introduction

The NIDDK conducts and supports research on many serious and costly diseases affecting the public health. Several diseases studied by the NIDDK are among the leading causes of disability and death in the Nation; all seriously affect the quality of life of those suffering from them. The economic burden of these diseases represents a major proportion of U.S. health care expenditures. A focus on basic research has traditionally guided the Institute's programs. A fundamental understanding of biologic systems will ultimately explain the abnormalities underlying disease and thus is imperative for the development of the most effective strategies for prevention and therapy. In addition to basic research, the Institute has a strong commitment to transfer new knowledge of biologic processes into appropriate clinical studies, and ultimately, into efforts to transmit knowledge and effective technologies to practicing physicians.

The NIDDK's Division of Diabetes, Endocrinology, and Metabolic Diseases is responsible for extramural research and research training related to diabetes mellitus; endocrinology, including osteoporosis; and metabolic diseases, including cystic fibrosis; this Division also supports research on obesity, as it is associated with type 2 diabetes. The Division of Digestive Diseases and Nutrition has responsibility for managing research programs related to liver and biliary

diseases; pancreatic diseases; gastrointestinal diseases, including motility, immunology, and digestion in the gastrointestinal tract; nutrient metabolism; and obesity, eating disorders, and energy regulation. The Division of Kidney, Urologic, and Hematologic Diseases supports research on the normal and disease processes of the kidney, genitourinary tract, and the blood-forming organs to improve or develop preventive, diagnostic, and treatment methods. The Division of Intramural Research conducts research and training within the Institute's laboratories and clinical facilities in Bethesda, Maryland, and Phoenix, Arizona. Shared interests in the biochemical and genetic processes underlying disease link the programs and divisions of the Institute, while close communication between the NIDDK and other NIH programs also fosters a confluence of fundamental knowledge in these vital areas of investigation.

Science Advances

Genetics and Genomics

Integration of Diverse Molecular Signals in the Brain Regulating Appetite and Body Size:

Obesity is a growing problem in the U.S. and is also a serious risk factor for type 2 diabetes. A number of studies indicate that choices about food intake are not all made at a conscious level. The regulation of appetite – and the control of body weight – are under the influence of a highly complex network of molecular signaling molecules through which a range of diverse tissues and organs communicate with each other. A hormone (a particular type of signaling molecule) can influence the activity of cells that make a specific “receptor” protein to “receive” the hormone and relay its signal into the cell; cells that lack a receptor for a particular hormone will not be directly affected by that hormone. By studying hormones and receptors, scientists have shed light on the molecular control of appetite in the brain. In one study, researchers genetically engineered mice to delete their “M3 muscarinic” receptors; they found that the mice ate less than normal and were lean. Interestingly, the deletion of these receptors resulted in a downstream effect on a hormone called MCH, reducing its levels. Since MCH normally increases food intake, its reduced levels could explain why the mice ate less. Consistent with this finding, other mice engineered to manufacture excess MCH became obese; they also became resistant to the effects of another hormone – insulin. Researchers studying other receptors, such as the insulin receptor, and other signaling proteins, such as leptin (which modulates eating), gained further insights into the molecular control of appetite and obesity. These data indicate a high degree of integrated communication through a web of signaling pathways converging in the brain, particularly in a part of the brain called the hypothalamus, to prompt eating or not eating. These studies also open new avenues for research into ways to combat obesity by targeting the molecules that control appetite.

Mouse Models of Insulin Resistance: Type 2 diabetes affects about 90-95 percent of the 16 million Americans with diabetes and is associated with obesity. When the body does not respond effectively to insulin, a condition called “insulin resistance” develops which can progress to diabetes. Insulin regulates blood glucose (sugar) levels by promoting glucose uptake into muscle and fat cells and suppressing glucose production by the liver. To further understand this process, investigators genetically engineered mice to have mutations that would eliminate, or “knock out,” the function of a protein, GLUT4, that transports glucose into cells. Recent technology allowed the scientists to remove GLUT4 only from fat cells, rendering them

unresponsive to insulin-induced glucose uptake, but leaving the insulin signaling apparatus intact in other tissues such as muscle and liver. Surprisingly, the lack of GLUT4 in fat cells not only made these cells insulin-resistant, but also made the muscle and liver insulin-resistant. After further experiments, the scientists concluded that fat cells may communicate with the liver and muscles to regulate glucose levels. These and other recent advances demonstrate the enormous contributions of knockout mouse genetic models to our understanding of disease, and also point to as yet undiscovered signaling molecules that may prove targets for potential new drugs for diabetes and obesity.

Uncoupling Proteins - A New Way to Burn Fat? Clinical studies have demonstrated that diet and exercise are effective treatments for both obesity and type 2 diabetes. However, many individuals are unable to adhere to these types of treatment programs or find them only minimally effective. Research on “uncoupling proteins” may provide new tools to aid these individuals in their struggle with weight gain. Just as an automobile uses some of the energy from burning fuel to run, while giving off some energy as heat, components of living cells called mitochondria convert nutrients from food into energy needed for bodily functions and into heat to maintain body temperature. If more calories are consumed than are required for energy and body temperature, the body stores the excess calories as fat. Mitochondrial proteins called uncoupling proteins steal some of the energy produced by burning nutrient fuel and release it as heat. In recent research on genetically engineered mice, scientists learned that uncoupling proteins are important in the regulation of blood sugar levels and weight gain, and thus are relevant to diabetes (in which blood sugar is poorly controlled) and obesity. Other investigators suggest that common genetic variations in an uncoupling protein might influence differences in human susceptibility to weight gain. With further understanding of uncoupling proteins, it may be possible to search for drugs that manipulate levels of these proteins to shunt excess calories into heat, rather than fat production, and thus prevent or control obesity and diabetes.

Gene Linked To Kidney Disease Caused by Diabetes: Kidney disease is the major cause of excess illness and premature death in people with type 1 diabetes. Recently, researchers identified a genetic variant in the apolipoprotein E gene in type 1 diabetics that is associated with a three-times greater risk of developing kidney disease. While previous investigations linking this variant with diabetic kidney disease were inconclusive, the present research is perhaps the most definitive to date. Future research will aim to determine how this apolipoprotein E variant causes increased risk of kidney disease.

A New Way to Prevent Blood Transfusion Reactions: Blood transfusions save the lives of accident victims, surgery patients, and people suffering from blood disorders such as sickle cell anemia. However, patients can develop an adverse reaction to transfused blood if certain molecules displayed on the surface of the donor blood cells differ from those on the patient’s own cells. There are many groups of such surface molecules, including the group used to classify blood into the A, B, or O types. A different blood group, the Dombrock group, is also important. A reaction against a surface molecule of the Dombrock group can cause the destruction of transfused blood cells as well as fever, chills, and other symptoms. However, reliable products have not been available to screen blood for Dombrock type. Recently, investigators used genomic

techniques to discover the gene coding for the Dombrock molecules. With this breakthrough, gene-based methods can now be developed to screen patients, and also donor blood, for Dombrock type to reduce painful transfusion reactions.

Protein Folding in Amyloid Disease – Implications for Therapy: A recent study of the disease familial amyloid polyneuropathy explained an intriguing case of two molecular wrongs making a right. The disease is caused by a mutant version of the protein transthyretin. People have two copies of the gene for transthyretin, one from each parent. If one copy codes for a protein with a mutation called “V30M,” and the second copy is normal, then disease occurs. Curiously, individuals are protected from disease if the second copy of the transthyretin gene – rather than being normal – has a different mutation, called “T119M.” Scientists recently discovered how the T119M mutation overcomes the adverse effects of the V30M mutant. Transthyretin proteins usually snap together in groups of four, but the V30M mutation renders them unable to maintain this normal configuration. Separated from the group, the individual proteins with the V30M mutation begin to unfold, lose their characteristic shape, and then aggregate in a harmful mass that interferes with nerve and muscle function. By contrast, scientists found that proteins with the T119M mutation exert an especially stabilizing influence on the transthyretin group, even if the foursome includes some of the V30M mutants. The implications of this finding are that this amyloid disease – and potentially others like it, such as Alzheimer’s – may be amenable to treatment strategies designed to stabilize the proper groups of proteins to prevent misfolding.

Developmental Biology

Alternatives To Pancreatic Islets - Stem Cells and Bioengineering: Type 1 diabetes is a disease in which the immune system destroys insulin-producing beta cells within the pancreas. People with this disease require lifelong insulin replacement to control blood sugar levels for survival, but current methods of insulin replacement are not a cure for type 1 diabetes. In a recent promising study, patients given transplants of human pancreatic islets (groups of cells that contain insulin-producing beta cells) from donor organs have remained free of the need for external insulin administration for over a year. Because donor organs are in limited supply, scientists are exploring other sources of insulin-producing cells. In one method, scientists propose coaxing stem cells to develop (or “differentiate”) into insulin-producing pancreatic cells. Pluripotent stem cells are cells that can differentiate into many types of cells and that also produce more stem cells. Recently, scientists found progenitor cells in both human and rat adult pancreas which can differentiate into all of the cell types of the pancreas. Another research group used a different strategy to generate insulin-producing cells: they engineered intestinal cells in mice to produce insulin in a regulated fashion similar to that of beta cells. While these studies are preliminary, they point to new areas of research which may facilitate development of a cure for type 1 diabetes.

Surprisingly Broad Potential Fates for Adult Stem Cells: The identification of stem cells in adult tissues and the discovery of ways to induce them to turn into different types of cells could provide a vital resource of cells for use in repairing damaged tissue and organs. Previously, it was thought that adult stem cells could differentiate into only a limited range of cell types. In several new studies, investigators have now demonstrated that adult stem cells have much greater plasticity. In animal studies, they found that stem cells from bone marrow, called

hematopoietic stem cells, can differentiate not only into blood cells, but also into liver cells and cells of other organs. Stem cells from the adult mouse pancreas can also differentiate into liver cells. Together, these findings suggest a previously unappreciated diversity of potential fates for adult stem cells.

Umbilical Cord Stem Cells for Transplantation: Among potential sources of stem cells is blood from the umbilical cord. This cord connects a mother to her fetus during pregnancy; it is not needed after birth. Umbilical cord stem cells have advantages over other sources of blood stem cells, such as bone marrow. For example, they are a perfect match for the child to whom they were connected, thus eliminating the need for finding a matching donor, which is especially difficult in minority populations who are under-represented in the National Marrow Donor Program. However, the number of stem cells in the umbilical cord is usually insufficient for successful transplantation of recipients who have a large body mass. Recently, scientists developed a new technique for growing these delicate cells in the laboratory to help them divide and produce more stem cells. This knowledge could lead to the development of systems for obtaining large numbers of cord stem cells for use in clinical research.

Harnessing Technology

A New Way to Monitor the Progression of Polycystic Kidney Disease: Polycystic kidney disease (PKD) is an inherited disease characterized by progressive kidney enlargement and kidney failure. Until recently, doctors had no rigorous approach to judge whether or not a PKD patient is likely to develop kidney failure and how quickly the disease may progress. A new study has examined the use of computed tomography scans as a way to monitor progression of the disease based on kidney size and the number of kidney cysts. Use of computed tomography scans will also enable doctors to judge how well potential treatments work by monitoring the size of kidneys and kidney cysts.

Non-Invasive Technique to Detect Hypoglycemia in Patients with Diabetes: The importance of intensive blood glucose (sugar) control to dramatically reduce the complications of diabetes was clearly demonstrated by two clinical trials: The Diabetes Control and Complications Trial, for type 1 diabetes, and the United Kingdom Prospective Diabetes Study, for type 2 diabetes. Patients currently use finger pricks to obtain blood samples for glucose monitoring, but this technique causes discomfort and can miss potentially dangerous episodes of hypoglycemia (low blood sugar), especially during sleep. A recent study found that the GlucoWatch biographer (Cygnus, Redwood City, CA) allows more effective detection of hypoglycemia than that achieved with current medical practice. The GlucoWatch biographer is a non-invasive device that automatically pulls glucose through the skin every 20 minutes and measures it with an electrochemical biosensor; it also provides low-glucose alerts. This device, whose development was made possible by multi-disciplinary basic and clinical research, may become an important tool to help patients aggressively manage their diabetes, avoiding episodes of hypoglycemia.

Advances in Organ Transplantation – A Study of Anti-CD154 Antibody Therapy: When people are given an organ transplant, they also need to take medications to prevent their immune systems from “rejecting,” or attacking the new organ. A new agent has recently been developed that prevents organ rejection when tested in monkeys. This new agent is an anti-CD154

antibody. Significantly, anti-CD154 antibody therapy does not have the toxic side effects associated with conventional therapies, which cause general suppression of the immune system. Scientists recently designed a study to determine the most efficacious treatment regimen of this anti-CD154 antibody in a model of kidney transplant in monkeys. They found that the animals experienced marked rejection-free survival for a period of time in the absence of ongoing therapy following a course of anti-CD154 therapy as short as one month. Thus, although its effects did not last indefinitely, anti-CD154 antibody remains a promising agent with extraordinary efficacy.

Minority Health Disparities

Diabetes, obesity, hepatitis C, end stage renal disease, benign prostate disease and several other diseases within the NIDDK research mission place a disproportionately heavy burden on racial and ethnic minority groups. To intensify efforts to redress these disparities, the NIDDK has established a new Office of Minority Health Research Coordination, and the NIDDK is supporting research focusing on minority populations and will support initiatives in this area.

ACE Inhibitor Reduces Risk of Kidney Failure in African Americans with Hypertension: African Americans disproportionately suffer from kidney failure. The racial disparity is most striking in younger people: African Americans between the ages of 25-44 are 20 times more likely to develop hypertensive kidney failure than Caucasians^{1,2}. A major clinical trial, the African American Study of Kidney Disease and Hypertension (AASK), has found that taking an angiotensin converting enzyme (ACE) inhibitor reduces the risk of kidney failure. Further, the trial showed that while taking drugs called calcium channel blockers helps many patients control blood pressure and reduce the risk of stroke and heart disease, patients may need an ACE inhibitor to protect their kidneys. The scientists also recommend measuring urinary protein excretion to guide initial therapy selection.

Impaired Insulin Response in Offspring of Parents with Early Onset Type 2 Diabetes: Researchers studying Pima Indians, who are at particularly high risk of diabetes, gained insight into the factors that predispose members of this population to the disease. Diabetes is characterized by poorly controlled blood glucose caused by a deficiency in insulin activity. In Pima Indian families in whom at least one parent had early onset type 2 diabetes, adult children exhibited lower than normal insulin secretion in response to glucose. In addition to this genetic influence on insulin secretion, which can be inherited from either parent, the researchers further learned that the diabetic condition of the mother during pregnancy also affects the child. Based on this clinical data, the investigators suggested that strategies to improve insulin secretion would be useful, and they emphasized the need for early diagnosis and treatment of diabetic symptoms during pregnancy.

¹ United States Renal Data System. USRDS 1999 Annual Data Report, National Institutes of Health, National Institute of Diabetes, Digestive, and Kidney Diseases, Bethesda, MD; 1999.

² Klag MJ, et al. Blood pressure and end-stage renal disease in men. N Engl J Med. 334:13-18, 1996.

Diabetes

Improved Long-Term Survival for Patients with Type 1 Diabetes: Before the introduction of insulin as a treatment for diabetes in the 1920s, the onset of type 1 diabetes – usually in childhood – meant almost certain death. To determine whether subsequent technological and therapeutic advances have had an impact on the long-term survival of people with type 1 diabetes, researchers recently examined mortality rates within the Allegheny County (Pennsylvania) Registry of patients. The patients were divided into three groups based on time of diagnosis. The study found a major improvement in long-term survival of people diagnosed with type 1 diabetes in more recent years. Improved survival was seen in both male and female patients, and in both African Americans and Caucasians, but death rates remained substantially higher in African Americans. The improvements roughly correlate with the introduction of better methods of assessing glucose control and self-monitoring equipment and with advances in blood pressure therapy in the 1980s. Follow-up studies will document whether survival continues to improve over time, which could suggest strategies to further increase survival, and address the racial disparities in survival.

Control of Glucose Production in the Liver by the Protein PGC-1: The healthy body maintains exquisite control over levels of glucose in the blood. During periods of fasting, the liver manufactures glucose for cells, especially brain cells, to use as a necessary source of energy. Likewise, after eating, insulin signals the liver to turn down its glucose production, and maintain blood glucose levels within a very narrow range. However, in patients with type 1 and type 2 diabetes, the liver often produces and releases excessive glucose into the blood, which left unchecked, leads to devastating consequences. Recently, scientists have discovered that the protein PGC-1 plays a pivotal role in glucose production by the liver. When glucose is needed, a set of hormones signal the liver to turn on the production of PGC-1, which in turn interacts with other factors that together turn on a series of genes required to produce glucose. In normal mice, PGC-1 is present in the liver - but only when glucose production is needed. In contrast, diabetic mice appear to make PGC-1 continuously. These results are the first demonstration that PGC-1 functions in glucose production by the liver, and have important implications for the treatment of diabetes. The anti-diabetes drug, metformin, shuts down glucose production in the liver, but exactly how it does this remains unknown. These new findings open new avenues for investigation that may lead to insights into the mechanism of action of metformin and other anti-diabetes drugs, and aid in the development of new and more effective drugs for use in the treatment of diabetes.

Reducing the Risk of Heart Disease in Women with Type 2 Diabetes: Type 2 diabetes affects 90-95 percent of the estimated 16 million Americans with diabetes. Among its devastating effects is an increased risk of heart disease, which is two to four times more common in diabetics than in non-diabetic adults. Women with diabetes are particularly at risk for heart disease. A recent analysis of data from the Nurses' Health Study revealed a dramatically increased death rate from heart disease associated with type 2 diabetes in women. Diabetes, in fact, confers nearly the same risk of death from heart disease as a previous heart attack. In other studies, researchers found that exercise can markedly reduce this risk. The American Diabetes Association, the National Diabetes Education Program, and the National Cholesterol Education Program now

recommend aggressive management of cardiovascular risk factors in diabetic patients to control cholesterol and high blood pressure and address such other risks as smoking and obesity. These new epidemiological findings provide important insights into the prevention of cardiovascular complications of type 2 diabetes.

Exposure to Diabetes in the Womb Increases Offspring's Risk of Diabetes and Obesity: Babies born to mothers with diabetes have an increased risk of becoming diabetic and obese themselves, but it has not been clear whether this is solely due to the genes inherited by the children, or whether the diabetic condition of the mother also plays a role. In a new study, researchers looked at families in which one child was born before and another after their mother's diagnosis with diabetes. The children born after their mothers had developed diabetes were more likely to be diabetic and obese themselves. Thus, the diabetic condition of the mother during pregnancy appears to affect a child's risk of diabetes and obesity. Since type 2 diabetes is increasingly occurring in younger women, the results of this study are particularly important, suggesting that prevention of diabetes in women of child-bearing age improves not only their health, but also the health of their offspring.

Story of Discovery: The Ominous Link Between Obesity and Type 2 Diabetes

Americans are facing an epidemic of obesity and type 2 diabetes, according to epidemiologic studies. Type 2 diabetes, a devastating illness already afflicting 90 to 95 percent of the 16 million people who have diabetes^{3,4}, can lead to serious complications including blindness, kidney failure, lower limb amputations, and heart disease. Although genetic factors may predispose a person to be overweight or develop diabetes, other factors must also be involved, because our genes could not possibly have changed quickly enough to account for the rapid increase in the prevalence of obesity and type 2 diabetes. Research indicates that the obesity problem, essentially, results from Americans eating too much and exercising too little. But how is an increase in obesity related to an increase in diabetes? For a long time, scientists have known that obese or overweight people are far more likely to develop type 2 diabetes; in fact, 80 percent of patients with type 2 diabetes are overweight or obese. However, only recently have scientists begun to find the biological molecules that connect these two health problems.

Type 2 diabetes develops through a multi-stage process. First, the body becomes unable to use insulin effectively, a condition known as insulin resistance. Insulin is a protein made by cells in the pancreas called beta cells. Insulin normally helps the body maintain a healthy level of the sugar glucose in the blood by causing fat and muscle cells to store glucose and by reducing glucose production in liver cells. When insulin resistance develops, the beta cells try to compensate by making more insulin. For a while, this helps keep blood glucose levels relatively normal, but eventually the beta cells become exhausted and cannot produce enough insulin to overcome the insulin resistance. At this point, individuals develop a condition called impaired glucose tolerance, in which blood glucose levels are higher than normal but not as high as those in diabetes. Left untreated, however, this condition frequently progresses to full-blown type 2 diabetes. Unfortunately people with insulin resistance and impaired glucose tolerance experience no outward symptoms and thus are unaware of this silent progression towards diabetes.

³ "National Institute of Diabetes and Digestive and Kidney Diseases." Diabetes Statistics. 19 December 2001 <<http://www.niddk.nih.gov/health/diabetes/pubs/dmstats/dmstats.htm#prev>>

⁴ "Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion." Diabetes Public Health Resource: National Diabetes Fact Sheet. 19 December 2001 <<http://www.cdc.gov/diabetes/pubs/facts98.htm#appendix>>

How is obesity connected to insulin resistance and diabetes? Clues are being found in unexpected places. Surprisingly, fat cells are not passive storehouses for fat, just keeping fat in case it is needed for energy. Instead, fat cells actively sense changes in energy availability and signal the brain and other tissues to regulate feeding and cellular processes. Scientists are learning that fat cells send out these signals in the form of special hormones, or signaling proteins, which the fat cells make and secrete. With the discoveries of novel signaling hormones, scientists are learning that the connection between fat and diabetes involves a complex balance of fat cell hormones.

Among the signaling proteins made by fat cells are leptin, resistin, and adiponectin (also known as Acrp30). After a meal, fat cells release leptin. This hormone signals the appetite-control center in the brain to stop eating. Scientists found that mice lacking the gene for leptin overeat and become obese. When given leptin, these mice lose weight – unfortunately, however, administering leptin to people does not effectively treat obesity. Thus, additional factors must also contribute to obesity.

Resistin, another fat cell signaling protein discovered recently, is so-named because too much of this hormone is thought to cause insulin resistance. When scientists gave mice a substance that inhibits resistin activity, their blood sugar level and insulin response improved. In fact, scientists initially discovered resistin as a result of some creative experiments to investigate how fat cells are affected by anti-diabetes drugs called TZDs, which are used to treat people. One of the results of adding a TZD drug to fat cells turns out to be decreased resistin production – and improved response to insulin. Thus, resistin itself might now be useful as a target for the discovery of new anti-diabetes drugs.

Another protein produced by fat cells, adiponectin, appears to connect obesity and diabetes in a way opposite to that of resistin – while too much resistin apparently causes insulin resistance, too little adiponectin may also be problematic. Scientists working on mouse models of obesity and type 2 diabetes recently found that giving extra adiponectin protein (made in the laboratory) to the mice caused them to become less insulin-resistant, lowering their blood glucose levels to near normal. In other experiments, when scientists gave mice a TZD drug, the type of diabetes drug that lowers resistin levels, they found that the drug can also increase adiponectin levels. From other research in mice, it appears that adiponectin helps muscle cells burn more energy; it also reduces body weight. In people, studies suggest that overweight and diabetic patients do not produce enough adiponectin. Thus, adiponectin may also be a good target for new therapies. In light of these studies, the ominous link between obesity and diabetes may be a balance of the levels of several fat cell signaling proteins with different effects. As more is learned about fat-cell signaling proteins, new drug therapies can be developed for obesity and diabetes.

While basic scientists are learning about what causes obesity and type 2 diabetes at the molecular level, clinical researchers are developing other measures to combat these conditions. Results from an exciting new study give us a way to battle the epidemic of obesity and type 2 diabetes. A major clinical study demonstrated that patients at risk of developing type 2 diabetes can prevent disease onset and improve their blood sugar through modest improvements in diet and exercise. These results are particularly important to minorities, who made up 45 percent of the study participants and are at increased risk of developing diabetes.

This study, called the Diabetes Prevention Program (DPP), identified overweight individuals suffering from impaired glucose tolerance, a condition which, as discussed above, increases the risk for type 2 diabetes. In the study, patients were assigned to one of three groups: intensive lifestyle intervention, medication, or placebo control. The lifestyle intervention had a goal of reducing body weight and staying active with a minimum of 30 minutes of exercise at least five times a week. The lifestyle intervention worked the best; patients in this group were 58 percent less likely to develop diabetes than those in the control group. Significantly, the intensive lifestyle intervention was highly effective for both genders and all ages and racial/ethnic groups in the study. Patients in the medication group, who received the diabetes drug metformin, were 31 percent less likely to develop diabetes than the control group, and they also lost weight. Metformin, while less effective overall in reducing the risk of diabetes, was effective in both genders and in all the racial and ethnic groups, which included African-Americans, Hispanic Americans, Asian Americans, and American Indians. In contrast to the lifestyle intervention, however, which was highly effective for all age and weight groups, metformin was not as effective among patients who were less overweight and was not effective in people over 60. This landmark study showed that with instruction and encouragement, patients at high

risk for diabetes could be successful in improving their diet and activity, with these relatively modest changes having a major impact in reducing the onset of diabetes.

Endocrine and Metabolic Diseases

Safe and Effective Therapy for Fabry Disease: Fabry disease is a rare genetic disorder mostly affecting males. It is caused by a deficiency of the enzyme α -galactosidase A; the lack of this enzyme causes life-threatening problems. This year, researchers realized a major advance in treatment, which had previously been limited to managing pain and end-stage complications of kidney disease, heart disease, and stroke. In two clinical trials, investigators demonstrated that giving laboratory-made α -galactosidase A enzyme to patients resulted in heart and kidney improvements. Thus, some of the severe complications of Fabry disease now appear amenable to treatment.

Digestive Diseases and Nutrition

Altered Brain Activity in Patients with Irritable Bowel Syndrome: People with irritable bowel syndrome have a colon that seems to respond strongly to stimuli that would not bother most individuals. To study this enhanced perception of stimuli, researchers measured brain activity during anticipated and actual rectal stimulation. In comparison to healthy individuals, irritable bowel syndrome patients showed more activity in regions of the brain that process negatively charged emotions and had reduced blood flow to specific circuits of the brain. These insights will lead to further areas of research into this syndrome, for which the cause is yet unknown.

Story of Discovery: Genetic Breakthroughs in the Study of Crohn's Disease

In a landmark finding, researchers announced the discovery of the first gene that confers susceptibility to Crohn's disease, a debilitating form of inflammatory bowel disease affecting an estimated 500,000 Americans. A targeted, interdisciplinary collaboration between scientists from different fields revealed that a mutated form of a gene called *NOD2* significantly increases a person's risk for developing Crohn's disease. This discovery is built upon research into how genetic and environmental factors combine to initiate an aberrant immune response that cascades into a destructive inflammation of the digestive system.

Crohn's disease typically afflicts young people in their teens and twenties, although it can strike at any age – as President Dwight Eisenhower discovered in his 60's. Symptoms include intestinal inflammation, nutritional deficiencies, abdominal pain, diarrhea, and rectal bleeding. For decades, the only treatment was surgical removal of the affected regions of the intestine. While research has since made possible less drastic alternatives, including oral medication and nutritional supplements, the majority of Crohn's patients still require surgery even today.

A complex interplay of environmental and genetic factors cause Crohn's disease. The environmental component involves the benign bacteria that normally live in our intestines. In healthy people these bacteria do not incite an attack by the immune system, but the immune system of patients with Crohn's disease reacts abnormally against these innocuous bacteria, unleashing destructive inflammation. Evidence for a genetic component comes from research on families in which individuals have the disease. Crohn's disease appears to be genetically complex, involving two or more genes, thus making the hunt for genes involved especially challenging. Research into the genetic and environmental causes of Crohn's disease could lead to the design of novel therapies and new methods for identifying individuals at risk for developing the disease, facilitating early intervention.

Important clues about the genetic and environmental factors underlying Crohn's disease have emerged from studies in animals. In an innovative study, scientists identified a variety of genes in healthy mice that were turned on or off in response to the presence of normal intestinal bacteria. This new knowledge of the response of healthy gut tissue to harmless bacteria may help scientists understand how this response goes awry in Crohn's disease. For insights into the destructive immune response of Crohn's disease, scientists studied mice known as SAMP1/Yit mice, which are genetically predisposed to developing Crohn's-like intestinal inflammation. When these animals are housed in special "germ-free" conditions they remain disease-free, demonstrating that genetic factors alone will not produce the disease. However, in the presence of normal environmental bacteria, SAMP1/Yit mice develop intestinal inflammation that remarkably mimics that of human Crohn's disease. The inflammation in the mice appears to be mediated by immune system cells called "T cells". These cells produce a protein called TNF- α which promotes inflammation. This work also further validates the use of SAMP1/Yit mice as a model of Crohn's disease because a drug used to treat many Crohn's patients, infliximab (Remicade®), also blocks TNF- α activity.

A major advance in unraveling the genetics of Crohn's disease occurred in 1996, when researchers identified a region on human chromosome 16 believed to include Crohn's disease genes. Other scientists, using cutting-edge genetic technology called DNA microarrays, also identified chromosome areas linked to Crohn's disease.

Research took a giant leap forward this past year with the discovery of the first susceptibility gene for Crohn's disease on chromosome 16. The impetus for this discovery was research in another field on an immune gene called *NOD1*. When a draft sequence of the human genome was released last year, the scientist who led the team that discovered *NOD1* noticed a very similar gene – *NOD2* – in a region of chromosome 16 previously linked to Crohn's disease. He pointed this out to a colleague who was studying Crohn's disease, and together they used her repository of DNA from 416 families with a history of Crohn's disease to identify a defective form of *NOD2* in about 15 percent of Crohn's patients. The mutated gene also is present in about eight percent of healthy people, indicating that other factors must also interact for the disease to occur. The discovery of *NOD2* mutations in Crohn's disease was validated by a second independent study using a completely different approach, known as positional cloning, to hunt for Crohn's disease genes on chromosome 16. In this second study, additional mutations in *NOD2* were found in Crohn's patients. Having one flawed copy of the gene doubles a person's chances of developing Crohn's; having two copies can increase the risk from 15 to 40 fold. Scientists are now investigating the function of the protein encoded by the *NOD2* gene, and have learned that it activates a molecular factor involved in the response to bacteria. Future studies will attempt to define how mutations in *NOD2* contribute to Crohn's disease.

Extensive research by dedicated scientists and clinicians, coupled with critical advances in technology, have provided the groundwork for extraordinary achievements in genetic research. Scientists studying animal models of Crohn's disease gained insights into the intertwined roles of the immune system of genetically susceptible individuals and naturally-occurring intestinal bacteria in promoting inflammation. The availability of the complete human genome sequence was pivotal in the identification of the first Crohn's disease gene, as was open communication between researchers working in different fields. Finding this gene is a crucial step toward conquering this disease.

A Model to Predict Survival in Patients with End-Stage Liver Disease – Applicability to Organ Allocation: Efforts to enhance the efficiency and effectiveness of the Nation's organ transplantation programs have focused on a variety of considerations. A congressionally commissioned report from the Institute of Medicine and an independent study recently concluded that waiting time was not an appropriate measure to use, recommending instead the development of a system based on medical factors and likely disease outcome. To develop such a system for liver allocation, scientists looked to the Model for End-Stage Liver Disease (MELD). Although this system was originally designed only for a specific liver medical procedure, the scientists found that MELD is generalizable to assess the severity of a wide range of liver disease and is verifiable, easy to use, and otherwise advantageous over a previous

system. This study thus validates MELD as applicable to the recommended criteria for future equitable organ allocation.

Genetic and Environmental Risk Factors for Primary Biliary Cirrhosis: Primary biliary cirrhosis is an uncommon liver disease marked by an abnormal immune reaction against the body's own proteins ("autoimmune"). It primarily affects women and ultimately leads to liver failure. Researchers recently surveyed patients, their siblings, and their friends for medical and lifestyle information to uncover potential risk factors. Based on the information obtained, the disease may be influenced by genetic susceptibility, and infection may help trigger the disease. Primary biliary cirrhosis is also associated with smoking. The discovery of both genetic and environmental risk factors will direct future research toward better understanding this disease.

Causes of Hereditary Pancreatitis: Hereditary pancreatitis is a rare disease of the pancreas. A mutation in a particular gene required for pancreatic function can cause the disease, even if only one copy of the gene is mutated. However, not everyone with a disease-causing mutation in this gene actually develops the disease. To investigate why, researchers compared different people with known hereditary pancreatitis mutations. Surprisingly, the incidence of disease within sets of identical twins raised together was the same as that in sets of unrelated individuals. Because identical twins – but not unrelated individuals – share most types of genetic factors and environmental factors, these factors alone cannot explain why these mutations do not always cause disease. Discovering the nature of other factors involved may lead to new therapies.

Breast Feeding May Limit Teenage Obesity: Over the past several decades, the number of overweight and obese children, adolescents, and adults has greatly increased. Obese adolescents are more at risk for potential heart disease, lower self-esteem, and other adverse conditions. Because being overweight can lead to obesity and is hard to treat, prevention is extremely important. Clinicians and scientists found in a recent study that infants who were fed breast milk more than infant formula and who were breast-fed longer were less likely to be overweight during childhood and adolescence. Thus, breast feeding may help prevent obesity.

Kidney, Urologic, and Hematologic Diseases

What Causes Polycystic Kidney Disease? The kidneys of patients who have polycystic kidney disease (PKD) gradually enlarge and stop working properly. Fluid-filled cysts grow and "squeeze out" the normal kidney tissue. Researchers celebrated a major achievement when they identified two genes that, when mutated, cause this disease. Recently, scientists determined the normal function of these genes, knowledge that is essential to understanding how the genetic abnormality in PKD results in clinical symptoms. The normal genes code for proteins called polycystin-1 and polycystin-2, which interact to form a channel in cell membranes. Entry of calcium through this channel into a kidney cell sets off a chain of signals that controls cell growth and promotes normal kidney function. In patients with the disease, the mutant versions of these proteins do not form the channel, thus affecting calcium entry, signaling, and kidney function. This vital information could lead to development of new treatment approaches.

Kidney Dialysis May Shorten the Survival of Subsequent Kidney Transplant Grafts: Patients who receive kidney transplants live longer than similar patients who undergo long-term dialysis.

Among adults in the U.S. who receive kidney transplants, approximately one-fourth have not had prior long-term dialysis. Whether kidney dialysis affects subsequent kidney transplant graft survival has been controversial. In a recent study, researchers found that transplanted kidneys lasted longer when given to patients at an early point in the disease, before a need for dialysis had arisen. While this observation will need to be confirmed by other studies, the data suggest that it may be better for a patient with end-stage kidney failure to receive a kidney transplant before long-term dialysis is initiated.

Genetic Link Discovered for IgA Nephropathy: End-stage kidney failure is a major health problem in the U.S., affecting hundreds of thousands of people. A principal cause of end-stage kidney failure is inflammation of the tiny tubes in the kidney that help clean the blood of waste and extra fluid. The most common form of this inflammation is called IgA nephropathy. While IgA nephropathy is not normally thought of as a genetic disease, studies in ethnic groups and families hinted at a possible genetic component. In a recent analysis of genome-wide scans of families from the U.S. and Italy, scientists found a region on chromosome 6 that is very strongly associated with IgA nephropathy and may confer susceptibility to the disease. Based on these findings, investigators will now try to identify the IgA nephropathy susceptibility gene, as it may provide insight into the disease process, diagnosis, and treatment.

Bladder Cancer Diagnosed by a Simple Urine Test: There is currently no simple, approved test for bladder cancer, but scientists recently developed a urine test that may be useful for this purpose. The key to the test is a protein called “survivin.” Survivin inhibits the normal cell death that occurs in the body as new cells are formed, and it is thought that abnormal survival of mutated cells leads to cancer. Survivin is made by cancer cells and released into urine, but it is not made by most normal cells. Thus, scientists developed a screen for survivin in urine as a sign of cancer. Their test was very sensitive, detecting survivin in all of the bladder cancer patients studied. It also gave very few false-positives and was simple and cost-effective. With this advance, a noninvasive urine test for bladder cancer may become routine.

Urinary Tract Infections: Emergence of a New of Multi-drug Resistant E. coli Strain: Urinary tract infections (UTIs) caused by *E. coli* bacteria affect 11 percent of women annually⁵. The widespread overuse of antibiotic drugs has led to increased incidence of multiple-drug resistance in *E. coli*, including those strains that can cause UTIs. Multiple-drug resistance severely limits the efficacy of existing antibiotics to treat infection. Responding to a sharp increase in drug-resistant UTIs, researchers recently identified a new strain of *E. coli*, called clonal group A, in urine samples from women with UTIs in California, Michigan, and Minnesota. Clonal group A was responsible for both 10 percent of the total UTIs and 38 to 51 percent of the drug-resistant UTIs observed in the patient groups, a surprisingly high prevalence for a single strain. Importantly, the distinct geographic clusters of the patient groups studied suggest a common

⁵ Manges AR, et al. Widespread Distribution of Urinary Tract Infections Caused by a Multi-drug Resistant *Escherichia coli* Clonal Group. N Engl J Med 345:1007-1013, 2001.

route of dissemination of clonal group A, possibly through food. This advance stresses that molecular typing of the *E. coli* causing drug-resistant UTIs may provide important information about the origins and spread of these bacteria within communities, enhancing opportunities to prevent further transmission of drug-resistant infections.

Story of Discovery: Bacterial Pili – Molecular Initiators of Bladder and Kidney Infections

It starts with an ill-fated “handshake” between two molecules of almost infinitesimally small size: a tiny bacterial protein grabs onto a small cluster of sugars on the surface of a human cell. From this molecular interaction arise millions of doctor visits each year. A urinary tract infection – which may involve the bladder, kidneys, or both – begins when a molecule on the tip of a hair-like projection from the surface of a bacterial cell recognizes and latches onto a molecule on the surface of its target cell, giving the bacteria a foothold in the urinary tract. Bladder and kidney infections are important public health concerns because many individuals suffer recurrent infections, and bladder infections can progress to more serious kidney infections. Recently, scientists in the field of structural biology – the study of the shape of molecules and how they interact with one another – uncovered important insights into the earliest stages of urinary tract infections and provided fresh evidence that strategies to block the attachment of bacteria to human cells may be an effective way to block the initial infections and prevent their recurrence.

Over 20 years ago, scientists began finding clues that proteins on the surface of bacteria may let the bacteria stick, or “adhere”, to human cells, such as urinary tract cells. Since that time, researchers have discovered many bacterial proteins and cloned and sequenced the genes that encode them. However, the sequences of genes tell only part of the story. Genes are sets of instructions for assembling a chain of building blocks, called amino acids, into a specific sequence to form a protein. But functional proteins do not exist as linear chains of amino acids – rather, the amino acid chains fold up, assuming intricate shapes with highly complex topography. To truly understand how a protein functions, and how it interacts with other proteins, it is often necessary to understand how a cell turns on genes that encode needed proteins, and what three-dimensional forms these proteins ultimately assume.

Among the people looking for this knowledge are scientists using tools of genetics, molecular biology, and structural biology. Structural biologists have long studied the assembly of proteins using bacterial pili as a model system. Pili are tiny rod-shaped projections from the surface of many bacteria that can help the bacteria adhere to other cells. Structural biologists have determined how bacteria begin assembly of a set of protein subunits into a pilus and transport the elongated pilus to the outer surface of the bacterial cell. Geneticists and molecular biologists have studied the genes that encode these protein subunits and other proteins involved in this process. However, pili are important for reasons beyond their value as models of protein assembly.

In urinary tract infections, the initial attachment of bacteria to the human cells that line the urinary tract is carried out in large part by structures on the surface of the bacterium – including pili – that recognize and stick to specific molecules on the surface of human cells. How do bacteria “turn on” their pili genes? The genes for some pili are controlled by a small segment of DNA located nearby. This small element doesn’t just stay put; it “flips” its relative orientation within the chromosome. When it faces one direction, the pili genes are turned “on” so that these pili can be made; in the opposite direction (“off”), the genes are turned off. To learn how the orientation of this invertible element might change during an actual infection, and what the implications of these changes could be, scientists recently isolated different types, or “strains”, of *E. coli* from cystitis (bladder infection) or pyelonephritis (kidney infection). The scientists examined whether the bacteria would change the orientation of this element during an infection of mice, starting in the “off” position. The cystitis (bladder infection) strain quickly flipped the element to “on”; in contrast, the pyelonephritis-causing bacteria (kidney infection) mostly left the element “off”. These pili, then, are apparently more critical for bladder infection. The results also illustrate how turning a gene on or off can influence the site of infection in the urinary tract.

Pili are also important in kidney infection. At the tip of another kind of pilus is a protein called PapG. PapG recognizes a human molecule called globoside, which contains a specific group of sugars, on the surface of a kidney cell. The bacteria uses this pilus to attach itself to the kidney cell by latching onto globoside with PapG. Scientists

have deduced the three-dimensional structure of PapG alone and PapG attached to globoside. This molecular snapshot – capturing details smaller than a millionth of a millimeter – allowed researchers to locate which regions of the PapG protein interact with which parts of the globoside. These structural details of a key event in infection may lead to the development of vaccines that target the disease process at its earliest stages.

While these studies brought insight into the initial stages of infection, other research highlights a role for pili in a different aspect of urinary tract infection: its recurrence. Why urinary tract infections recur in a significant number of women has long remained a mystery. New research suggests that bacteria use their pili not only for sticking to cells initially, but also for getting inside of these cells. Once inside, the bacteria could hide out, remaining in the body after an initial infection only to emerge later and cause a subsequent urinary tract infection. Further insights into the role of pili in this process might allow the design of therapies to interrupt this cycle of infections.

The study of bacterial pili illustrates how technical and highly specialized research into a seemingly obscure question – how proteins are assembled in bacteria and what shapes they take – can be relevant to a common and costly health issue: urinary tract infections. From bacterial protein assembly to possible targets for future therapies, the story of pili shows that there is no such thing as something too small to investigate.

Highlights of Planned Activities

Diabetes, Endocrinology, and Metabolic Diseases: The NIDDK plans to build upon initiatives in basic and clinical research. With respect to type 1 diabetes, the Institute's Intramural scientists in the NIDDK/Navy Transplantation and Autoimmunity Branch are continuing research on islet transplantation in humans; preliminary studies appear promising. Additionally, the NIDDK is co-sponsoring the Immune Tolerance Network initiative, which is spearheaded by the National Institute on Allergy and Infectious Diseases (NIAID), for research to replicate the results of the "Edmonton Protocol" for islet transplantation. Other research will include, for example, an oral insulin study of the Diabetes Prevention Trial for Type 1 Diabetes, for which recruitment has begun. Investigators have also convened meetings to plan clinical studies on type 1 diabetes as part of TrialNet. The NIDDK plans to investigate ways in which interventions that have already been demonstrated to be beneficial by laboratory or clinical investigations can be extended or adapted to larger populations to improve health care delivery and diabetes self-management and to promote healthy lifestyles to reduce the risk of diabetes and obesity. To continue to build fundamental knowledge that could eventually lead to novel ideas for diabetes care, the NIDDK will develop a Beta Cell Biology Consortium to focus on research on beta cell and pancreas development; this could also include study of human embryonic stem cells in accordance with criteria established by the Administration. The NIDDK will also support studies on an important group of proteins called orphan receptors. To advance research on diabetes and related areas of endocrinology and metabolism, the NIDDK will strive to expand diabetes research centers to bring together clinical and basic science investigators from relevant disciplines.

Digestive Diseases and Nutrition: The NIDDK will continue its efforts to combat obesity as a serious health problem and as a risk factor for type 2 diabetes. To this end, the NIDDK will study environmental approaches toward preventing weight gain, focusing on individual, family, group, or community environments. The NIDDK will also pursue further genetic insights into inflammatory bowel disease. Additionally, further research on the development of the gut, liver,

and pancreas is planned; these studies may identify useful markers and models for studying disease. The NIDDK will also pursue new insights into the epidemiology of and mechanisms responsible for Barrett's esophagus, a condition that can lead to cancer. The NIDDK will continue to bolster research into non-alcoholic steatohepatitis, a common liver disease, and biliary atresia, the most common reason for liver transplantation in children, by developing databases for these diseases and forming a clinical research network for non-alcoholic steatohepatitis and a clinical research consortium for biliary atresia. The NIDDK plans to assess the recently-developed adult-to-adult living donor liver transplantation procedure by studying outcomes to obtain information that will aid decisions by physicians, patients, and potential donors.

Kidney, Urologic, and Hematologic Diseases: To examine risk factors that predict rapid decline in kidney function and the causes of accelerated cardiovascular disease in patients with kidney disease, NIDDK is launching a prospective cohort study in patients with chronic renal insufficiency. Based on the recommendations of a task force convened by the NIDDK and the American Society of Pediatric Nephrology, an initiative will be undertaken to evaluate immunosuppressive treatments for focal segmental glomerulosclerosis. NIDDK is planning to establish a cooperative group of investigators to design and implement trials of new treatments for polycystic kidney disease. The NIDDK also plans to begin studies to compare minimally invasive surgical therapies for benign prostatic hyperplasia. Studies are also beginning to use biological samples available as a result of the NIDDK-supported clinical trial on Medical Therapies of Prostatic Symptoms to identify biological markers associated with benign prostatic hypertrophy and/or prostate cancer. The NIDDK will strive for further understanding of blood cells with research on hematopoietic stem cells in a genome anatomy project; this could include possible support for human embryonic stem cell research in accordance with criteria established by the Administration.

Trans-NIDDK and Trans-NIH: In response to recommendations by a working group of experts brought together by the NIDDK and the National Institute of Mental Health and by a conference held in January 2001, the NIDDK will undertake research to better understand the association of depression with diabetes, renal disease and obesity. Because abnormalities in membrane transport processes underlie such diseases as diabetes and cystic fibrosis, the NIDDK plans innovative research into membrane transport with the use of non-mammalian model organisms that are easily experimentally manipulated. Additionally, the NIDDK continues to support a range of trans-NIH activities including major genetic cross-cutting initiatives. The NIDDK will extend the Genome Anatomy Projects it recently established in conjunction with the National Cancer Institute through an initiative to study how progenitor cells lead to the development and maintenance of tissues and organs; this could include possible support for human embryonic stem cell research in lines approved by the Administration. The NIDDK will build upon progress in the trans-NIH effort to develop genomic and informatics tools for studying the zebrafish, a powerful model organism for investigating genes and development. The NIDDK will also continue to support ongoing research on illness and bacteria that can be acquired from food. With a new medical student research training program linked to NIDDK-supported Centers, the NIDDK will strive to reverse the decline in the number of physician scientists engaged in biomedical research.

AIDS: In collaboration with the National Heart, Lung, and Blood Institute, the NIDDK will support an initiative to develop strategies for treating metabolic complications associated with the highly active anti-retroviral therapy used to treat HIV infection. These complications represent risk factors for diabetes, cardiovascular disease, and other diseases.

Minority Health Disparities: The NIDDK is planning a diabetes-focused science education effort in Tribal middle and high schools to increase the presence of American Indians in the biomedical sciences. The NIDDK will also support the formation of centers for expanded clinical studies of type 2 diabetes in children, which disproportionately affects minority groups. To strengthen the training of biomedical researchers and better draw upon diverse sources of talent, the NIDDK will co-sponsor, with many other Institutes at the NIH, an initiative on education in clinical research for minority students; the NIDDK will also support a medical student research scholars program for members of underrepresented minority groups.

Educational Programs: Through a variety of educational programs, the NIDDK will continue to provide important health information to health practitioners and the public. For example, the National Diabetes Education Program (NDEP), which is a partnership between the NIDDK, the CDC, and over 200 public and private organizations, is disseminating the results of a major clinical trial, the Diabetes Prevention Program. The NDEP will develop a new public health campaign based on the findings of this clinical trial. The trial demonstrated that modest weight loss has a major impact on delaying the onset of diabetes in those at risk for this disease, including men and women of all ages and all ethnic groups studied. The trial also found that treatment with the oral diabetes drug metformin (Glucophage®) also reduces diabetes risk, though less dramatically, in people at high risk for type 2 diabetes. This year, the NDEP launched a campaign to promote the control of risk factors for heart disease in people with diabetes: “Be Smart About Your Heart.” The campaign’s call to action is “Control the ABCs of Diabetes,” with A for the hemoglobin A_{1c} test that measures blood sugar levels, B for blood pressure, and C for cholesterol. The NIDDK has initiated the National Kidney Disease Education Program. The Program’s goals are to enhance awareness about the seriousness of kidney disease; the importance of prevention, early diagnosis, and appropriate management of kidney disease; and the prevention and management of complications. The Program is in development, with several meetings having been held to review the current state of kidney disease in the U.S., to assess the impact of the disease on the populations at greatest risk, and to obtain recommendations from experts on the design of the education program. A steering committee has been established. Next steps toward implementation of the Program include convening work groups to address the Program’s priority activities, and finalizing a strategic plan. The NIDDK will also continue its Weight-control Information Network (WIN), which produces and provides materials on obesity, weight control, and nutrition. On October 20, 2001, WIN launched the "Sisters Together: Move More Eat Better" campaign with a Fun Walk for African American women in the District of Columbia.

Other Areas of Interest

The NIDDK will continue vigorous support of its clinical trials programs. A new initiative that will facilitate additional clinical research on type 1 diabetes is the Type 1 Diabetes TrialNet.

Spearheaded by the NIDDK and co-sponsored by the NIAID and NICHD, the TrialNet will include clinical centers, recruitment networks and a coordinating center. It will provide the research infrastructure needed to foster the future design and execution of pilot studies and expanded clinical research. The TrialNet will permit more rapid clinical testing of novel approaches to treatment and prevention. The TrialNet will also enable efficient performance of intervention studies to preserve pancreatic beta cell function in new-onset cases of type 1 diabetes, and ultimately to prevent onset of the disease. In addition, the TrialNet will allow for completion of the Diabetes Prevention Trial for Type 1 Diabetes (DPT-1). The DPT-1 is an ongoing clinical trial to determine whether use of oral insulin in non-diabetic relatives of persons with type 1 diabetes can delay the development of diabetes.

In the area of type 2 diabetes, the NIDDK will initiate clinical trials for the primary prevention and treatment of the disease in children. Primary prevention trials will focus on cost-effective, school- or community-based interventions with the potential for broad, population-wide application. Treatment trials may include lifestyle changes and/or pharmacologic therapy. It is anticipated that trials will be undertaken at multiple sites to ensure an adequate sample size as well as geographic and racial/ethnic diversity.

The recently launched Look AHEAD (Action For Health in Diabetes) multi center, randomized clinical trial will study the effects of a lifestyle intervention designed to achieve and maintain weight loss over the long term through decreased caloric intake and exercise. Specifically, the trial will examine the effect of lifestyle interventions on heart attack, stroke and cardiovascular-related death.

In order to prevent the development of cirrhosis and liver cancer in people with chronic hepatitis C, the NIDDK initiated a large-scale clinical trial studying long-term antiviral treatment with the drugs interferon (in a new form) and ribavirin. This multicenter clinical trial, called HALT-C (Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis) is directed at non-responders to optimal standard therapy of hepatitis C. Ancillary studies have been developed to complement this trial in such areas as non-invasive assessment of liver fibrosis, early detection of liver cancer, and how best to manage long-term therapy of this disease.

People with kidney disease from high blood pressure have a better chance of reducing the risk of kidney failure if they take an angiotensin-converting enzyme (ACE) inhibitor. Results from the *African American Study of Kidney Disease and Hypertension (AASK)* found that the ACE inhibitor ramipril slowed kidney disease by 36 percent and cut the risk of kidney failure and death by 48 percent in patients who had at least a gram of protein in the urine. While calcium channel blockers help many patients, particularly African Americans, control blood pressure and reduce the risk of stroke and heart disease, these results show that patients may need an ACE inhibitor to protect the kidneys. In the *Hemodialysis* trial, researchers are determining the effects of different hemodialysis regimens on morbidity and mortality in end-stage kidney failure patients. Newly launched studies include the *Cohort Study of Chronic Renal Insufficiency*, a prospective longitudinal study that will examine genetic, environmental, behavioral, nutritional, quality of life, and health resource utilization factors in patients with chronic kidney disease. The Institute is also initiating FAVORIT, a clinical trial to determine whether lowering homocysteine levels with folate and vitamin B supplementation reduces mortality in kidney

transplant patients. Two ongoing projects, the *Interstitial Cystitis Clinical Trials Group* and the *Chronic Prostatitis Collaborative Research Network* are moving into established interventional treatment trials. The *Prostatitis Network* has added new clinical facilities to strengthen the recruitment of African American men with chronic prostatitis, and is conducting studies of innovative approaches to treating chronic prostatitis. The NIDDK is leading an NIH-wide effort to develop a network of multidisciplinary clinical centers and a biostatistical coordinating center, the *Urinary Incontinence Treatment Network*, that will focus on a trial to identify the most effective surgical treatment strategies for women with urinary incontinence. Final results are expected this year from the clinical trial on *Medical Therapy of Prostate Symptoms* which assesses the optimum drug therapy for benign prostatic hypertrophy.

Innovations in Management and Administration

The NIDDK is strengthening its long-range planning with the establishment of three trans-NIDDK strategic planning groups on the following topics: (1) Genetics, Genomics and Bioinformatics; (2) Stem Cells and Developmental Biology; and (3) Disease Prevention and Management. Each group consists of National Advisory Council members, other scientists external to the NIH, and NIDDK administrative leaders. The groups are providing advice on formulating initiatives to capitalize on scientific opportunities and to meet public health needs. The NIDDK will also enhance its grants and contracts management functions and fiduciary responsibilities through refinements in electronic record-keeping and data analysis, including development of an NIDDK Intranet and reorganization of various administrative functions.

AIDS

Positive and Negative Consequences of Highly Active Antiretroviral Therapy: Current therapy for HIV infection usually involves a multi-drug regimen known as highly active antiretroviral therapy (HAART) that includes an HIV protease inhibitor. Prolonged HAART is associated with a potentially serious metabolic syndrome that may result in the redistribution of body fat from the extremities to the trunk, lipid abnormalities, and elevated insulin levels, insulin resistance, or diabetes. The cause of this syndrome is unknown, but it is thought to be a complex physiological response to the antiretroviral drug regimen. HIV-infected adults treated with HAART who develop metabolic changes may display elevated levels of specific enzymes that are associated with an increased risk of adverse cardiovascular events. Treatment of these patients with metformin, an anti-diabetes drug, reduces their elevated insulin levels and also lowers the levels of circulating enzymes, suggesting that this treatment may lower the risk of cardiovascular events. On a molecular level, the protease inhibitor indinavir seems to inhibit the ability of muscle cells to import glucose from the blood, which may partly explain why HAART can result in abnormally high blood glucose and insulin levels in some patients. Another protease inhibitor, nelfinavir, inhibits the differentiation of immature fat cells and promotes the death of already-mature ones, suggesting one possible mechanism for HAART-associated changes in body fat distribution. Although HAART is associated with metabolic complications, it nevertheless represents a beneficial therapy for children with HIV, resulting in improvement of several growth parameters, including weight, weight-for-height, and arm muscle circumference compared to their status prior to protease inhibitor therapy.

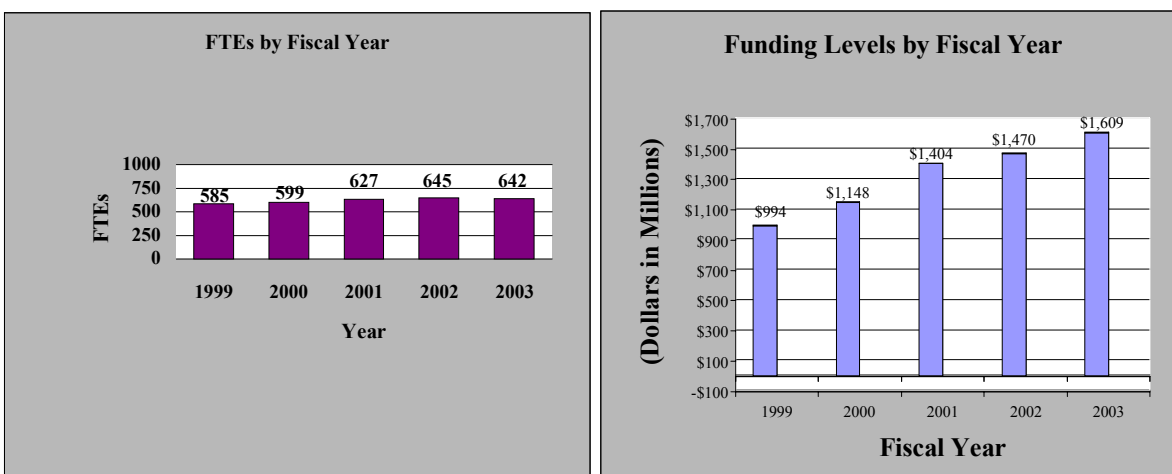
Budget Policy

The Fiscal Year 2003 budget request for the NIDDK is \$1,609,292,000 including AIDS, an increase of \$138,477,000 and 9.4 percent over the FY 2002 level.

A 5 year history of FTEs and Funding Levels for NIDDK are shown in the graphs below. Note that Fiscal Years 2000 and 1999 are not comparable for the Managerial Flexibility Act of 2001 legislative proposal.

One of NIH's highest priorities is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. The Fiscal Year 2003 request provides average cost increases for competing RPGs equal to the Biomedical Research and Development Price Index (BRDPI), estimated at 4.0 percent. Noncompeting RPGs will be funded at committed levels which include increases of 3 percent on average for recurring direct costs.

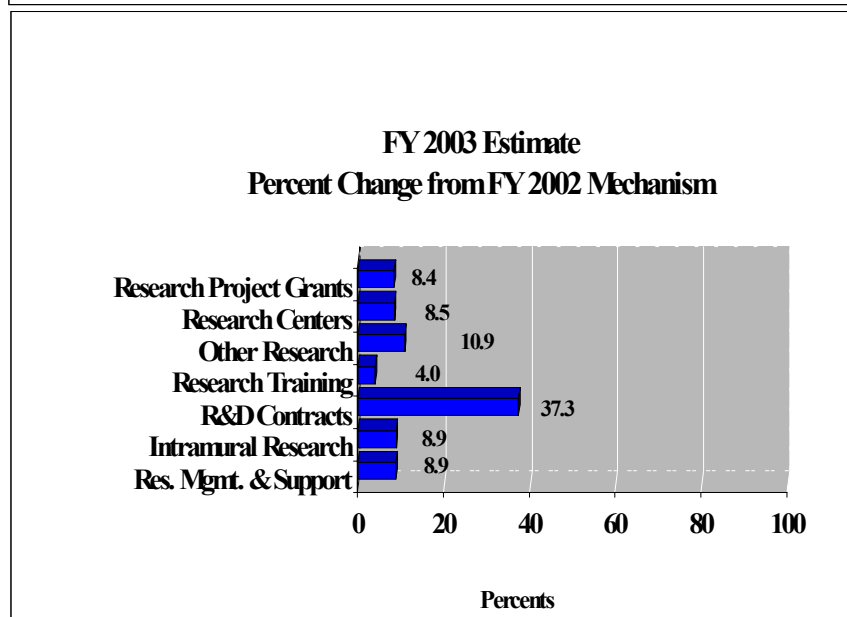
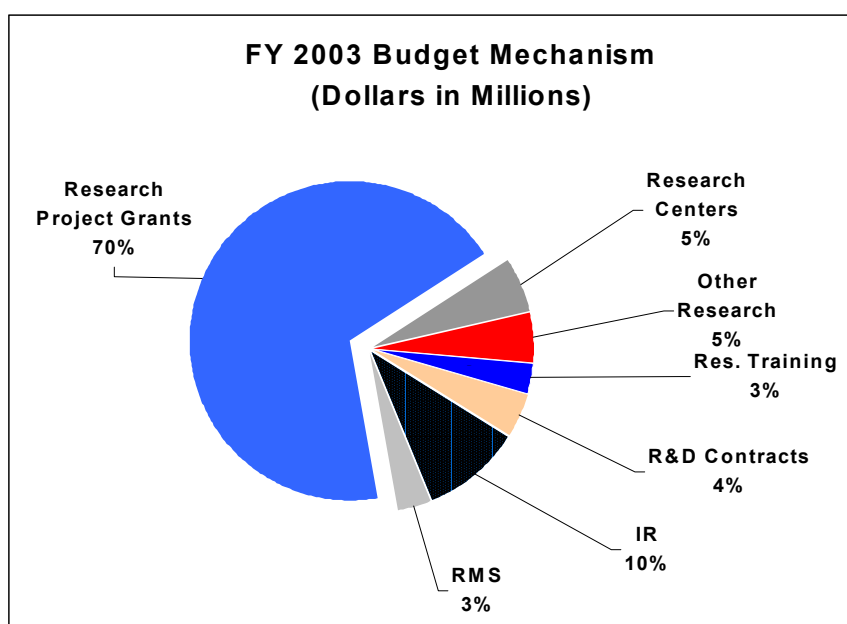
Future promises for advancement in medical research rest in part new investigators with new



ideas. In the Fiscal Year 2003 request, NIDDK will support 960 pre- and postdoctoral trainees in full-time training positions, the same number as in FY 2002. Stipend levels for NRSA trainees will increase by 4 percent over Fiscal Year 2002 levels.

The Fiscal Year 2003 request includes funding for 77 research centers, 509 other research grants, including 12 clinical career awards, and 97 R&D contracts. The R&D contracts mechanism also includes support for 40 contracts for the Extramural Clinical and Pediatric Loan Repayment Programs. Intramural Research and Research Management and Support receive increases of 9 percent over FY 2002.

The mechanism distribution by dollars and percent change are displayed below:



NATIONAL INSTITUTES OF HEALTH

**National Institute of Diabetes and Digestive and Kidney Diseases
TOTAL - Current Law
Budget Mechanism**

MECHANISM	FY 2001 Actual		FY 2002 Appropriation		FY 2002 Current Estimate		FY 2003 Estimate		2003/2002 % Change	Avg. Cost % Change
Research Grants:	No.	Amount	No.	Amount	No.	Amount	No.	Amount		
<u>Research Projects:</u>										
Noncompeting	2074	\$654,799,000	2067	\$719,047,000	2067	\$719,047,000	2190	\$785,061,000	9.2	
Administrative supplements	(262)	29,368,000	(150)	10,500,000	(150)	10,500,000	(150)	10,500,000	0.0	
<u>Competing:</u>										
Renewal	229	76,562,000	270	94,404,000	270	94,404,000	280	101,388,000	7.4	
New	472	174,125,000	525	169,295,000	525	169,295,000	545	181,820,000	7.4	
Supplements	2	364,000	2	365,000	2	365,000	2	365,000	0.0	
Subtotal, competing	703	251,051,000	797	264,064,000	797	264,064,000	827	283,573,000	7.4	3.5
Subtotal, RPGs	2777	935,218,000	2864	993,611,000	2864	993,611,000	3017	1,079,134,000	8.6	
SBIR/STTR	111	29,052,000	143	37,542,000	143	37,542,000	140	38,290,000	2.0	
Subtotal, RPGs	2888	964,270,000	3007	1,031,153,000	3007	1,031,153,000	3157	1,117,424,000	8.4	
<u>Research Centers:</u>										
Specialized/comprehensive	98	76,841,000	73	79,373,000	73	79,373,000	77	86,123,000	8.5	
Clinical research	0	0	0	0	0	0	0	0	0.0	
Biotechnology	0	0	0	0	0	0	0	0	0.0	
Comparative medicine	0	9,225,000	0	0	0	0	0	0	0.0	
Research Centers in Minority Institutions	0	0	0	0	0	0	0	0	0.0	
Subtotal, Centers	98	86,066,000	73	79,373,000	73	79,373,000	77	86,123,000	8.5	
<u>Other Research:</u>										
Research careers	324	37,159,000	386	46,113,000	386	46,113,000	417	50,413,000	9.3	
Cancer education	0	0	0	0	0	0	0	0	0.0	
Cooperative clinical research	0	0	0	0	0	0	0	0	0.0	
Biomedical research support	0	0	0	0	0	0	0	0	0.0	
Minority biomedical research support	0	1,663,000	0	3,378,000	0	3,378,000	0	3,628,000	7.4	
Other	65	28,654,000	84	19,920,000	84	19,920,000	92	22,920,000	15.1	
Subtotal, Other Research	389	67,476,000	470	69,411,000	470	69,411,000	509	76,961,000	10.9	
Total Research Grants	3375	1,117,812,000	3550	1,179,937,000	3550	1,179,937,000	3743	1,280,508,000		
<u>Training:</u>	<u>FTEs</u>		<u>FTEs</u>		<u>FTEs</u>		<u>FTEs</u>			
Individual awards	157	6,212,000	157	6,833,000	157	6,833,000	157	7,107,000	4.0	
Institutional awards	856	34,669,000	803	41,222,000	803	41,222,000	803	42,870,000	4.0	
Total, Training	1013	40,881,000	960	48,055,000	960	48,055,000	960	49,977,000	4.0	
Research & development contracts (SBIR/STTR)	70 (10)	73,605,000 (905,000)	76 (9)	50,993,000 (906,000)	76 (9)	50,540,000 (906,000)	97 (20)	69,408,000 (2,000,000)	37.3	
Intramural research	<u>FTEs</u> 431	126,899,000	<u>FTEs</u> 444	141,768,000	<u>FTEs</u> 444	141,768,000	<u>FTEs</u> 444	154,527,000	9.0	
Research management and support	196	40,601,000	201	46,080,000	201	46,080,000	198	50,227,000	9.0	
Cancer prevention & control	0	0	0	0	0	0	0	0	0.0	
Construction		0		0		0		0	0.0	
Total, NIDDK	627	1,399,798,000	645	1,466,833,000	645	1,466,380,000	642	1,604,647,000	9.4	
(Clinical Trials)		(128,563,000)		(141,928,000)		(141,928,000)		(152,807,000)		

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases
TOTAL - Accrued Costs for Retirement and Health Benefits
Budget Mechanism

MECHANISM	FY 2001 Actual		FY 2002 Appropriation		FY 2002 Current Estimate		FY 2003 Estimate		2003/2002 % Change	Avg. Cost % Change
	No.	Amount	No.	Amount	No.	Amount	No.	Amount		
Research Grants:										
Research Projects:										
Noncompeting										
Administrative supplements										
Competing:										
Renewal										
New										
Supplements										
Subtotal, competing										
Subtotal, RPGs										
SBIR/STTR										
Subtotal, RPGs										
Research Centers:										
Specialized/comprehensive										
Clinical research										
Biotechnology										
Comparative medicine										
Research Centers in Minority Institutions										
Subtotal, Centers										
Other Research:										
Research careers										
Cancer education										
Cooperative clinical research										
Biomedical research support										
Minority biomedical research support										
Other										
Subtotal, Other Research										
Total Research Grants										
Training:										
Individual awards										
Institutional awards										
Total, Training										
Research & development contracts (SBIR/STTR)										
	<u>FTEs</u>		<u>FTEs</u>		<u>FTEs</u>		<u>FTEs</u>			
Intramural research	0	2,826,000	0	3,060,000	0	3,060,000	0	3,205,000	4.7	
Research management and support	0	1,270,000	0	1,375,000	0	1,375,000	0	1,440,000	4.7	
Cancer prevention & control	0	0	0	0	0	0	0	0	0.0	
Construction									0.0	
Total, NIDDK	0	4,096,000	0	4,435,000	0	4,435,000	0	4,645,000	4.7	
(Clinical Trials)		(0)		(0)		(0)		(0)		

NATIONAL INSTITUTES OF HEALTH

**National Institute of Diabetes and Digestive and Kidney Diseases
TOTAL - Proposed Law
Budget Mechanism**

MECHANISM	FY 2001 Actual		FY 2002 Appropriation		FY 2002 Current Estimate		FY 2003 Estimate		2003/2002 % Change	Avg. Cost % Change
	No.	Amount	No.	Amount	No.	Amount	No.	Amount		
Research Grants:										
<u>Research Projects:</u>										
Noncompeting	2074	\$654,799,000	2067	\$719,047,000	2067	\$719,047,000	2190	\$785,061,000	9.2	
Administrative supplements	(262)	29,368,000	(150)	10,500,000	(150)	10,500,000	(150)	10,500,000	0.0	
Competing:										
Renewal	229	76,562,000	270	94,404,000	270	94,404,000	280	101,388,000	7.4	
New	472	174,125,000	525	169,295,000	525	169,295,000	545	181,820,000	7.4	
Supplements	2	364,000	2	365,000	2	365,000	2	365,000	0.0	
Subtotal, competing	703	251,051,000	797	264,064,000	797	264,064,000	827	283,573,000	7.4	3.5
Subtotal, RPGs	2777	935,218,000	2864	993,611,000	2864	993,611,000	3017	1,079,134,000	8.6	
SBIR/STTR	111	29,052,000	143	37,542,000	143	37,542,000	140	38,290,000	2.0	
Subtotal, RPGs	2888	964,270,000	3007	1,031,153,000	3007	1,031,153,000	3157	1,117,424,000	8.4	
<u>Research Centers:</u>										
Specialized/comprehensive	98	76,841,000	73	79,373,000	73	79,373,000	77	86,123,000	8.5	
Clinical research	0	0	0	0	0	0	0	0	0.0	
Biotechnology	0	0	0	0	0	0	0	0	0.0	
Comparative medicine	0	9,225,000	0	0	0	0	0	0	0.0	
Research Centers in Minority Institutions	0	0	0	0	0	0	0	0	0.0	
Subtotal, Centers	98	86,066,000	73	79,373,000	73	79,373,000	77	86,123,000	8.5	
<u>Other Research:</u>										
Research careers	324	37,159,000	386	46,113,000	386	46,113,000	417	50,413,000	9.3	
Cancer education	0	0	0	0	0	0	0	0	0.0	
Cooperative clinical research	0	0	0	0	0	0	0	0	0.0	
Biomedical research support	0	0	0	0	0	0	0	0	0.0	
Minority biomedical research support	0	1,663,000	0	3,378,000	0	3,378,000	0	3,628,000	7.4	
Other	65	28,654,000	84	19,920,000	84	19,920,000	92	22,920,000	15.1	
Subtotal, Other Research	389	67,476,000	470	69,411,000	470	69,411,000	509	76,961,000	10.9	
Total Research Grants	3375	1,117,812,000	3550	1,179,937,000	3550	1,179,937,000	3743	1,280,508,000		
<u>Training:</u>										
Individual awards	157	6,212,000	157	6,833,000	157	6,833,000	157	7,107,000	4.0	
Institutional awards	856	34,669,000	803	41,222,000	803	41,222,000	803	42,870,000	4.0	
Total, Training	1013	40,881,000	960	48,055,000	960	48,055,000	960	49,977,000	4.0	
Research & development contracts (SBIR/STTR)	70 (10)	73,605,000 (905,000)	76 (9)	50,993,000 (906,000)	76 (9)	50,540,000 (906,000)	97 (20)	69,408,000 (2,000,000)	37.3	
Intramural research	FTEs 431	129,725,000	FTEs 444	144,828,000	FTEs 444	144,828,000	FTEs 444	157,732,000	8.9	
Research management and support	196	41,871,000	201	47,455,000	201	47,455,000	198	51,667,000	8.9	
Cancer prevention & control	0	0	0	0	0	0	0	0	0.0	
Construction		0		0		0		0	0.0	
Total, NIDDK	627	1,403,894,000	645	1,471,268,000	645	1,470,815,000	642	1,609,292,000	9.4	
(Clinical Trials)		(128,563,000)		(141,928,000)		(141,928,000)		(152,807,000)		

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases

Budget Authority by Activity 1/

(dollars in thousands)

ACTIVITY	FY 2001 Actual		FY 2002 Estimate		FY 2003 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:								
Division of Diabetes, Endocrinology and Metabolic Diseases		\$592,121		\$558,591		\$611,613		\$53,022
Division of Digestive Diseases and Nutrition		310,573		349,295		382,451		33,156
Division of Kidney, Urologic and Hematologic Diseases		329,604		370,646		405,829		35,183
Subtotal, extramural research		1,232,298		1,278,532		1,399,893		121,361
Intramural research	431	129,725	444	144,828	444	157,732	0	12,904
Research management and support	196	41,871	201	47,455	198	51,667	(3)	4,212
Total	627	1,403,894	645	1,470,815	642	1,609,292	(3)	138,477

1/ Please see the following tables for the crosswalk from current law to proposed law to reflect the administration's proposal for full accrued retirement and health benefits.

National Institutes of Health

National Institute of Diabetes and Digestive and Kidney Diseases

2001 Crosswalk for Accrued Retirement and Health Benefit Costs
(Dollars in thousands)

	<u>2001 Actual Current Law</u>	<u>2001 Additional Accrual Costs</u>	<u>2001 Actual Proposed Law</u>
Extramural Research:			
Division of Diabetes, Endocrinology and Metabolic Diseases	\$591,998		\$591,998
Division of Digestive Diseases and Nutrition	310,450		310,450
Division of Kidney, Urologic and Hematologic Diseases	329,481		329,481
Subtotal, extramural research	1,231,929		1,231,929
Intramural Research	126,899	2,826	129,725
Research management and support	40,970	1,270	42,240
Total	1,399,798	4,096	1,403,894

National Institutes of Health

National Institute of Diabetes and Digestive and Kidney Diseases

2002 Crosswalk for Accrued Retirement and Health Benefit Costs
(Dollars in thousands)

	2002 Current Estimate <u>Current Law</u>	2002 Additional <u>Accrual Costs</u>	2002 Appropriation <u>Proposed Law</u>
Extramural Research:			
Division of Diabetes, Endocrinology and Metabolic Diseases	\$558,591		\$558,591
Division of Digestive Diseases and Nutrition	349,295		349,295
Division of Kidney, Urologic and Hematologic Diseases	370,646		370,646
Subtotal, extramural research	1,278,532		1,278,532
Intramural Research	141,768	3,060	144,828
Research management and support	46,080	1,375	47,455
Total	1,466,380	4,435	1,470,815

National Institutes of Health

National Institute of Diabetes and Digestive and Kidney Diseases

2003 Crosswalk for Accrued Retirement and Health Benefit Costs
(Dollars in thousands)

	<u>2003 Estimate Current Law</u>	<u>2003 Additional Accrual Costs</u>	<u>2003 Estimate Proposed Law</u>
Extramural Research:			
Division of Diabetes, Endocrinology and Metabolic Diseases	\$611,613		\$611,613
Division of Digestive Diseases and Nutrition	382,451		382,451
Division of Kidney, Urologic and Hematologic Diseases	405,829		405,829
Subtotal, extramural research	1,399,893		1,399,893
Intramural Research	154,527	3,205	157,732
Research management and support	50,227	1,440	51,667
Total	1,604,647	4,645	1,609,292

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases
Summary of Changes

2002 Estimated budget authority				\$1,470,815,000
2003 Estimated budget authority				1,609,292,000
Net change				138,477,000
CHANGES	2002 Current Estimate Base		Change from Base	
	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:	0			
a. Within grade increase		\$51,817,000		\$611,000
b. Annualization of January 2002 pay increase		51,817,000		622,000
c. January 2003 pay increase		51,817,000		1,010,000
d. Payment for centrally furnished services		27,318,000		2,459,000
e. Increased cost of laboratory supplies, materials, and other expenses		62,633,000		1,849,000
f. Accrued costs for retirement and health benefits		3,060,000		145,000
Subtotal				6,696,000
2. Research Management and Support:				
a. Within grade increase		18,874,000		222,000
b. Annualization of January 2002 pay increase		18,874,000		226,000
c. January 2003 pay increase		18,874,000		368,000
d. Payment for centrally furnished services		5,204,000		468,000
e. Increased cost of laboratory supplies, materials, and other expenses		22,002,000		491,000
f. Accrued costs for retirement and health benefits		1,375,000		65,000
Subtotal				1,840,000
Subtotal, Built-in				8,536,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases
Summary of Changes--continued

CHANGES	2002 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	2067	729,547,000	123	66,014,000
b. Competing	797	264,064,000	30	19,509,000
c. SBIR/STTR	143	37,542,000	(3)	748,000
Total	3007	1,031,153,000	150	86,271,000
2. Centers	73	79,373,000	4	6,750,000
3. Other research	470	69,411,000	39	7,550,000
4. Research training	960	48,055,000	0	1,922,000
5. Research and development contracts	76	50,993,000	21	18,415,000
Subtotal, extramural				120,908,000
6. Intramural research	<u>FTEs</u> 444	141,768,000	<u>FTEs</u> 0	12,759,000
7. Research management and support	201	46,080,000	(3)	4,147,000
8. Construction		0	0	0
Subtotal, program		1,466,833,000		137,814,000
Total changes			(3)	146,350,000

National Institute of Diabetes and Digestive and Kidney Diseases
Budget Authority by Object

	FY 2002 Appropriation	FY 2002 Current Estimate	FY 2003 Estimate	Increase or Decrease	Percent Change
Total compensable workyears:					
Full-time employment	0	0	642	642	0.0
Full-time equivalent of overtime and holiday hours	0	0	0	0	0.0
Average ES salary	\$139,984	\$139,984	\$145,583	\$5,599	4.0
Average GM/GS grade	11.0	11.0	11.0	0.0	0.0
Average GM/GS salary	\$73,283	\$73,283	\$76,213	\$2,930	4.0
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	\$0	\$0	\$0	\$0	0.0
Average salary of ungraded positions	\$0	\$0	\$0	\$0	0.0
OBJECT CLASSES	FY 2002 Appropriation	FY 2002 Estimate	FY 2003 Estimate	Increase or Decrease	Percent Change
Personnel Compensation:					
11.1 Full-Time Permanent	\$28,360,000	\$28,360,000	\$29,354,000	\$994,000	3.5
11.3 Other than Full-Time Permanent	17,931,000	17,931,000	18,678,000	747,000	4.2
11.5 Other Personnel Compensation	1,400,000	1,400,000	1,450,000	50,000	3.6
11.8 Special Personnel Services Payments	10,900,000	10,900,000	11,500,000	600,000	5.5
11.9 Total Personnel Compensation	58,591,000	58,591,000	60,982,000	2,391,000	4.1
12.1 Personnel Benefits	12,100,000	12,100,000	12,500,000	400,000	3.3
12.1 Personnel Benefits, Accrued Retirement Costs	3,254,000	3,254,000	3,423,000	169,000	5.2
13.0 Benefits for Former Personnel	0	0	0	0	0.0
Subtotal, Pay Cost, Current Law	70,691,000	70,691,000	73,482,000	2,791,000	3.9
Subtotal, Pay Cost, Proposed Law	73,945,000	73,945,000	76,905,000	2,960,000	4.0
21.0 Travel and Transportation of Persons	2,620,000	2,620,000	2,775,000	155,000	5.9
22.0 Transportation of Things	480,000	480,000	510,000	30,000	6.3
23.1 Rental Payments to GSA	0	0	0	0	0.0
23.2 Rental Payments to Others	1,500,000	1,500,000	1,585,000	85,000	5.7
23.3 Communications, Utilities and Miscellaneous Charges	1,600,000	1,600,000	1,700,000	100,000	6.3
24.0 Printing and Reproduction	1,100,000	1,100,000	1,175,000	75,000	6.8
25.1 Consulting Services	2,124,000	2,124,000	2,247,000	123,000	5.8
25.2 Other Services	6,691,000	6,691,000	7,090,000	399,000	6.0
25.3 Purchase of Goods and Services from Government Accounts	99,500,000	99,500,000	105,000,000	5,500,000	5.5
25.3 Accrued Retirement Costs	1,181,000	1,181,000	1,222,000	41,000	3.5
25.4 Operation and Maintenance of Facilities	6,801,000	6,801,000	7,285,000	484,000	7.1
25.5 Research and Development Contracts	50,993,000	50,540,000	69,408,000	18,868,000	37.3
25.6 Medical Care	1,100,000	1,100,000	1,175,000	75,000	6.8
25.7 Operation and Maintenance of Equipment	2,100,000	2,100,000	2,220,000	120,000	5.7
25.8 Subsistence and Support of Persons	0	0	0	0	0.0
25.0 Subtotal, Other Contractual Services, Current Law	169,309,000	168,856,000	194,425,000	25,569,000	15.1
25.0 Subtotal, Other Contractual Services, Proposed Law	170,490,000	170,037,000	195,647,000	25,610,000	15.1
26.0 Supplies and Materials	14,478,000	14,478,000	15,171,000	693,000	4.8
31.0 Equipment	8,000,000	8,000,000	8,400,000	400,000	5.0
32.0 Land and Structures	0	0	0	0	0.0
33.0 Investments and Loans	0	0	0	0	0.0
41.0 Grants, Subsidies and Contributions	1,197,047,000	1,197,047,000	1,305,416,000	108,369,000	9.1
42.0 Insurance Claims and Indemnities	0	0	0	0	0.0
43.0 Interest and Dividends	8,000	8,000	8,000	0	0.0
44.0 Refunds	0	0	0	0	0.0
Subtotal, Non-Pay Costs, Current Law	1,396,142,000	1,395,689,000	1,531,165,000	135,476,000	9.7
Subtotal, Non-Pay Costs, Proposed Law	1,397,323,000	1,396,870,000	1,532,387,000	135,517,000	9.7
Total Budget Authority by Object, Current	1,466,833,000	1,466,380,000	1,604,647,000	138,267,000	9.4
Total Budget Authority by Object, Proposed	1,471,268,000	1,470,815,000	1,609,292,000	138,477,000	9.4
Total Accrued Retirement Costs	4,435,000	4,435,000	4,645,000	210,000	4.7

NATIONAL INSTITUTES OF HEALTH
National Institute of Diabetes and Digestive and Kidney Diseases
Salaries and Expenses

OBJECT CLASSES	FY 2002 Appropriation	FY 2002 Current Estimate	FY 2003 Estimate	Increase or Decrease	Percent Change
Personnel Compensation:					
Full-Time Permanent (11.1)	\$28,360,000	\$28,360,000	\$29,354,000	\$994,000	3.5
Other Than Full-Time Permanent (11.3)	17,931,000	17,931,000	18,678,000	747,000	4.2
Other Personnel Compensation (11.5)	1,400,000	1,400,000	1,450,000	50,000	3.6
Special Personnel Services Payments (11.8)	10,900,000	10,900,000	11,500,000	600,000	5.5
Total Personnel Compensation (11.9)	58,591,000	58,591,000	60,982,000	2,391,000	4.1
Civilian Personnel Benefits (12.1)	12,100,000	12,100,000	12,500,000	400,000	3.3
Accrued Costs of Retirement Benefits (12.1)	3,254,000	3,254,000	3,423,000	169,000	5.2
Benefits to Former Personnel (13.0)	0	0	0	0	0.0
Subtotal, Pay Costs, Current Law	70,691,000	70,691,000	73,482,000	2,791,000	3.9
Subtotal, Pay Costs, Proposed Law	73,945,000	73,945,000	76,905,000	2,960,000	4.0
Travel (21.0)	2,620,000	2,620,000	2,775,000	155,000	5.9
Transportation of Things (22.0)	480,000	480,000	510,000	30,000	6.3
Rental Payments to Others (23.2)	1,500,000	1,500,000	1,585,000	85,000	5.7
Communications, Utilities and Miscellaneous Charges (23.3)	1,600,000	1,600,000	1,700,000	100,000	6.3
Printing and Reproduction (24.0)	1,100,000	1,100,000	1,175,000	75,000	6.8
Other Contractual Services:					
Advisory and Assistance Services (25.1)	2,124,000	2,124,000	2,247,000	123,000	5.8
Other Services (25.2)	6,691,000	6,691,000	7,090,000	399,000	6.0
Purchases from Govt. Accounts (25.3)	64,044,000	64,044,000	66,919,000	2,875,000	4.5
Accrued Retirement Costs (25.3)	1,181,000	1,181,000	1,222,000	41,000	3.5
Operation & Maintenance of Facilities (25.4)	6,801,000	6,801,000	7,285,000	484,000	7.1
Operation & Maintenance of Equipment (25.7)	2,100,000	2,100,000	2,220,000	120,000	5.7
Subsistence & Support of Persons (25.8)	0	0	0	0	0.0
Subtotal, Other Contractual Services, Current Law	81,760,000	81,760,000	85,761,000	4,001,000	4.9
Subtotal, Other Contractual Services, Proposed Law	82,941,000	82,941,000	86,983,000	4,042,000	4.9
Supplies and Materials (26.0)	14,403,000	14,403,000	15,092,000	689,000	4.8
Subtotal, Non-Pay Costs, Current Law	96,163,000	96,163,000	108,153,000	11,990,000	12.5
Subtotal, Non-Pay Costs, Proposed Law	97,344,000	97,344,000	109,375,000	12,031,000	12.4
Total, Administrative Costs, Current Law	166,854,000	166,854,000	181,635,000	14,781,000	8.9
Total, Accrued Costs	4,435,000	4,435,000	4,645,000	210,000	4.7
Total, Administrative Costs, Proposed Law	171,289,000	171,289,000	186,280,000	14,991,000	8.8

National Institute of Diabetes and Digestive and Kidney Diseases

SIGNIFICANT ITEMS IN HOUSE AND SENATE APPROPRIATIONS
COMMITTEE REPORTS

FY 2002 House Appropriations Committee Report Language (H. Rpt.107-229)

Item

Bladder Disease – More than one of every ten Americans suffers from bladder disease. The Committee understands that NIDDK convened the Bladder Research Progress Review Group in 2001 and has issued an RFA related to urinary incontinence. The Committee urges NIDDK to finalize a long-term research strategy based on the recommendations of the progress review group. NIDDK is also urged to enhance research in such areas as basic bladder disease, pediatric urology and urinary tract infection through all available mechanisms, as appropriate, including establishing centers of excellence and maintaining a cell/tissue archive for bladder disease. The Committee requests that the Director of the Institute be prepared to report on the progress in this area at the fiscal year 2003 appropriations hearing. (p. 67)

Action Taken or to be Taken

The NIDDK is fully committed to research on bladder diseases, supporting basic, applied, and clinical research in many areas, including diseases and disorders of the bladder, urinary tract infections, urinary tract stone disease, and pediatric urology, including development of the urinary tract. To enhance progress in bladder disease research efforts, the Bladder Research Progress Review Group (Bladder Research PRG) meeting was convened in the summer of 2001. The PRG evaluated the bladder research portfolios of NIDDK and NIH, identified research opportunities, and defined unmet needs in bladder research. A strategic plan to redefine bladder research and to target specific areas for expansion is being formulated by the PRG. The report from this meeting is in final draft form and, once released, will be an invaluable guide for guiding NIDDK efforts in bladder disease research in the future.

In addition, the NIDDK is planning a conference on “Urinary Reflux and Obstructive Uropathy in Children” for the Spring of 2002. This conference aims to provide an up-to-date overview of basic and clinical knowledge of urinary reflux and obstructive uropathy in children, to determine areas in which additional basic and clinical research is needed, and to develop a research plan. To accomplish these objectives, the conferees will address many issues, including epidemiology, genetics, treatment strategies and outcomes, and effects on adult bladder function. In the summer of 2002, NIDDK also plans to host a symposium on the “Genetics of Complex Traits—Application to Common Urologic Disorders,” which will provide an expert overview of the genetics of complex traits, discuss the application of this knowledge to relevant urologic disorders, and develop a research agenda. Symposium participants will develop a research strategy, including applicable basic and clinical research specialties.

In support of completed, current, and future studies within its purview, the NIDDK has recently determined a need to establish a central NIDDK repository for biosamples and data collected in large, multi-center clinical studies. Having a central repository will expand the usefulness of these studies by providing access to the biosamples and data to a wider research community beyond the end of the study. It will also expedite the receipt of samples for analysis. As a first step, the NIDDK issued a Request for Information to solicit comments about the proposed repository, and held a meeting on November 28, 2001 to discuss the information received and to assist in the formulation of one or more Requests for Proposals to carry out the various tasks of the repository. The NIDDK already maintains an archive of tissue samples taken from patients with interstitial cystitis at the University of Pennsylvania. The recommendations of the Bladder Research PRG will be utilized to help the Institute determine how best to incorporate these specimens into the larger national archive resource.

Item

Cooley's Anemia – The Committee continues to support work to advance treatments for Cooley's anemia in the areas of iron measurement, fetal hemoglobin and iron chelation and encourages NIDDK to enhance research through all available mechanisms, as appropriate, including investigator-initiated research. The Committee requests that the Director of the Institute be prepared to provide a progress report at the fiscal year 2003 appropriations hearing. (p. 67)

Action Taken or to be Taken

The NIDDK strongly supports research that will benefit Cooley's anemia (thalassemia major) patients. Because of the excess iron build-up in the heart, liver, and kidneys of Cooley's anemia patients resulting from chronic transfusions and inappropriate intestinal iron absorption, development of an effective iron-chelating drug is of the highest priority. NIDDK's long-standing role in studies of candidate drugs is crucial because Cooley's anemia is a rare genetic condition and does not elicit significant private sector interest. An iron-chelating drug is in clinical use (DesferalR), but it is expensive, is not effective when taken orally, and must be administered parenterally *via* a pump over a 12-hour period daily. Within the past 24 months, pre-clinical toxicologic studies under a single NIDDK contract have investigated a parenterally effective iron-chelating compound, HBED, which can be administered in smaller volumes than Desferal. These studies are designed to support an Investigational New Drug Application that may be filed with the Food and Drug Administration by a pharmaceutical company (or other entity) for the purpose of initiating clinical trials to determine the safety and efficacy of the compound. To enhance these pursuits, the NIDDK has recently developed an initiative for planned implementation in 2002 that should identify a contractor to continue pre-clinical toxicologic evaluation of new candidate chelating drugs.

The buildup of excess iron in tissues is not only dangerous but also difficult to assess. At present, the technique of biomagnetic susceptibility employing a superconducting quantum interference device (SQUID) provides the only non-invasive method for quantitative measurement of tissue iron stores that has been calibrated, validated, and used in clinical studies. However, due to the complexity, cost, and technical demands of the liquid-helium-cooled

superconducting instruments now required, the method is available only at a limited number of locations nationally. Other techniques that have been suggested for development include magnetic resonance imaging and computed tomography. In April 2001, NIDDK, with support from the NIH Office of Rare Diseases, hosted a scientific workshop on “Noninvasive Measurement of Iron.” This workshop was organized to air issues involved in non-invasive iron measurement, and to assist the NIDDK in designing the most effective approaches to improve such measurement, including support for new techniques and studies to assess their value in guiding iron-chelating therapy for patients with Cooley’s and other anemias. Subsequently, a grant was awarded to develop a new generation of instruments to measure body iron magnetically, and other initiatives are planned to adapt magnetic resonance imaging (MRI) to the measurement of body iron.

Regarding fetal hemoglobin synthesis, the NIDDK, in response to a Request for Applications cosponsored with NHLBI, recently granted four awards to study transactivation of fetal hemoglobin genes for treatment of sickle cell disease and Cooley’s anemia. These studies are aimed at improving understanding of how fetal hemoglobin expression is controlled, and hence how it may be manipulated in adult patients as a therapeutic approach for these diseases.

Item

Diabetes – The Committee commends NIDDK for its leadership in implementing juvenile diabetes research. The Committee encourages NIDDK to enhance research in this area through all available mechanisms, as appropriate, including vaccine development, genomics/bioinformatics, research training and development of alternative sources of insulin-producing beta cells for therapeutic replacement. (p. 67)

Action Taken or to be Taken

The NIDDK is supporting a number of projects that will increase understanding of how and why insulin-producing beta cells are destroyed. This information is critical to development of an effective vaccine to prevent the autoimmune beta cell destruction that results in type 1 diabetes. The NIDDK co-sponsored an initiative with NIAID entitled “Non-Human Primate Immune Tolerance Cooperative Study Group (NHPCSG).” This multi-center research program will attempt to test new methods for preventing rejection of transplanted beta cells and to understand the causes of autoimmune destruction of pancreatic beta cells. The NIDDK and the Juvenile Diabetes Research Foundation International (JDRF) are also co-sponsoring the Immune Tolerance Network (ITN), a collaboration involving numerous research institutions and spearheaded by NIAID. The ITN will solicit, develop, implement, and address clinical strategies for the purpose of inducing and maintaining immune tolerance in patients receiving kidney and islet transplants. Along with NIAID, NCI, and the NIH Office of Research on Women’s Health, the NIDDK co-sponsored an initiative entitled “Infectious Etiology of Chronic Diseases: Novel Approaches to Pathogen Detection,” designed to identify possible infectious organisms responsible for causing chronic diseases such as type 1 diabetes. In a similar vein, the NIDDK-sponsored meeting, “Etiology and Epidemiology of Early Autoimmune Type 1 Diabetes in

Humans,” held on October 25-26, 2001, gathered investigators to explore ways to identify environmental “triggers” of type 1 diabetes. All of these efforts will build the solid knowledge foundation necessary to develop a successful vaccine to prevent type 1 diabetes.

The NIDDK currently supports a number of projects important for developing genomics/bioinformatics resources relevant to research on type 1 diabetes. Representative projects include: (1) The Functional Genomics of Endocrine Pancreas Project, which brings together expertise in pancreas development, DNA sequencing, and bioinformatics. These researchers are defining the genes expressed during development of the endocrine pancreas. They are also working to develop shared bioinformatics tools and reagents to aid in researching the role of these genes in the pathogenesis of type 1 diabetes. (2) The Type 1 Diabetes Genetic Consortium, which is a collaborative research effort to identify type 1 diabetes susceptibility genes through scanning human genome sequences in families with at least two children with type 1 diabetes. (3) In collaboration with NIAID, the NIDDK is supporting the International Histocompatibility Working Group (IHWG) in a project to study the histocompatibility genes that are the major genetic determinants of type 1 diabetes; these genes normally take part in the immune system’s recognition of “self,” but this recognition is subverted in the beta cells of the pancreas in an individual with type 1 diabetes, resulting in the autoimmune response that targets these cells. One of the projects that the IHWG is undertaking is to identify additional genetic differences in the histocompatibility region that contribute to type 1 diabetes. Such information may enable researchers to develop a set of genetic markers to reliably detect individuals at risk for developing type 1 diabetes. Future NIDDK initiatives in genetics/genomics/bioinformatics are being developed with the assistance of a trans-NIDDK Strategic Planning Group.

The NIDDK also provides considerable support for research training for those dedicated to conquering diabetes. The NIDDK, along with the American Diabetes Association (ADA) and the JDRF, issued a Request for Applications (RFA) in October 2001 to support research training for pediatric endocrinologists to address type 1 diabetes. This program will permit eligible institutions to support joint programs in research training and career development. The NIDDK has established a special career development award to provide research support for individuals who have completed their medical training and have dedicated themselves to becoming independent clinical researchers. The Institute will also participate in NIH-wide loan repayment programs in an effort to recruit physician scientists and pediatric researchers to the field of diabetes research. These programs repay a fixed amount of education loans in exchange for dedicated research commitments in the areas of pediatric and/or clinical research.

Replacement of lost insulin-producing pancreatic beta cells holds great promise as a treatment for type 1 diabetes. The NIDDK is sponsoring a number of conferences aimed at developing alternative sources of insulin-producing beta cells for therapeutic replacement. A recent NIDDK-sponsored workshop entitled “Pancreatic Development, Proliferation and Stem Cells” brought together investigators from multiple disciplines doing state-of-the-art research in developmental biology of the pancreas, beta cell biology, and stem cells. The focus of another meeting, “Beta Cell Biology in the 21st Century,” is recent progress in understanding beta cell biology and exciting new results in other systems that will impact future work in the beta cell. One of the

purposes of this meeting was to provide a forum to explore new research directions that derive from emerging genomic and proteomic information. Information and abstracts from the meeting can be reviewed at the website <www.betacellbiology.niddk.nih.gov>.

The NIDDK has actively encouraged research to provide the knowledge needed to develop alternative sources of insulin-producing beta cells for therapeutic replacement. In calendar year 2001, the Institute issued several RFAs in order to implement initiatives relevant to this research. The “Innovative Partnerships in Type 1 Diabetes Research” initiative encourages collaboration between researchers with expertise in type 1 diabetes and researchers whose expertise, while not in type 1 diabetes, is relevant to problems associated with type 1 diabetes. The hope is to encourage type 1 diabetes researchers to act as “talent scouts” to identify other researchers who could contribute to research breakthroughs. The “Bench to Bedside Research on Type 1 Diabetes and its Complications” initiative encourages collaboration between basic research scientists with expertise in type 1 diabetes and clinical scientists who can help to translate basic discoveries into pre-clinical or clinical treatment trials for patients with the disease. The “Comprehensive Programs in Beta Cell Biology” initiative has established a Beta Cell Biology Consortium and a Comprehensive Beta Cell Project, both of which are designed to bring trained investigators together to help gain a better understanding of beta cell development and differentiation. Another initiative, entitled “Gene Transfer Approaches to Enhance Islet Transplantation,” supports scientifically meritorious research applications to develop ways to increase the survival of transplanted pancreatic beta cells. If more transplanted cells survive, doctors will not have to use as many cells for each patient receiving a transplant. Thus, each donor pancreas could be used to treat more patients. By supporting these worthwhile research efforts, the NIDDK hopes to find ways to develop an unlimited supply of new beta cells or islets for use in long-term treatment of type 1 diabetes.

Item

Digestive Diseases – The Committee continues to encourage NIDDK to strike an appropriate balance between conducting basic studies on digestive diseases and bringing those research findings to the bedside in the form of improved patient care. (p. 68)

Action Taken or to be Taken

The NIDDK continues to strive to bring promising results of basic studies from the laboratory to the clinical setting. The Institute encourages grant applications using the small grant mechanism to foster innovative clinical and epidemiological research into new therapies. A current Program Announcement specifically encourages applications for pilot studies leading to full-scale clinical trials and epidemiological studies relating to digestive diseases. In particular, the Institute seeks research that is innovative and/or of potential high impact.

Item

Digestive Diseases (IBS) – The Committee commends NIDDK for its leadership in the area of inflammatory bowel disease (IBD). The Committee also remains concerned about the increasing frequency of irritable bowel syndrome (IBS), a chronic complex of disorders that malign the

digestive system and encourages NIDDK to enhance research for irritable bowel syndrome/functional bowel disorders through all available mechanisms, as appropriate, including education/scientific symposiums. The Institute is also encouraged to collaborate with CDC and the private sector on an IBS awareness campaign. (p. 68)

Action Taken or to be Taken

Irritable bowel syndrome (IBS) has been reported to be the most common disorder seen in the field of medicine dealing with digestive diseases in the United States. It has been estimated that IBS and other functional disorders affect over 15 percent of the population with a wide spectrum of symptoms, ranging from mildly distressing symptoms to disabling symptoms that have a negative impact on the quality of life.

Over the last decade there has been an increase in our understanding of the epidemiology of IBS, how this disease affects the body, and the burden of illness of this disorder. Significant research advances clearly demonstrate that the intestines of IBS patients are overly sensitive to various stimuli, including drugs, emotions, and certain foods. Additional research on the biological molecule serotonin in relationship to IBS symptoms has provided the opportunity to develop new therapies targeted to molecules that interact with serotonin in the gut.

In April 2001, at the International Symposium on Functional Bowel Disorders, NIDDK staff presented research opportunities for both basic and clinical research focused on improving our understanding of these disorders and the development of clinical trials to improve patient care. In August 2001, the NIDDK issued a Program Announcement encouraging exploratory grants (R 21s) in digestive diseases specifically examining motility disorders and the role of the nervous system of the intestine in disorders such as irritable bowel syndrome.

In addition, the NIDDK is working with the members of the research community to develop a conference on the topics of fecal and urinary incontinence, focusing on crosscutting physiologic and quality of life issues that have impacts on patients with IBS. The conference is planned for September 2002.

NIDDK funding for IBS has more than doubled in the past few years, from \$3.7 million in FY 1996 to \$9.3 million in FY 2001. In addition to the NIDDK's funding of research, the NIDDK National Digestive Diseases Information Clearinghouse published a new educational booklet in March 2001, entitled "What I Need To Know About Irritable Bowel Syndrome," which is written for a level of functional literacy (easy-to-read). The NIDDK will explore the opportunities for increasing public awareness of IBS with other agencies such as the CDC.

Item

Digestive Diseases (IBD) – The Committee recognizes the success of the Digestive Disease Centers program in addressing a wide range of disorders that result in significant human suffering and economic burden. The Committee continues to encourage NIDDK to expand this program with an increased emphasis on inflammatory bowel disease. (p. 68)

Action Taken or to be Taken

The NIDDK continues to give priority to basic and clinical research aimed at discovering the causes and better treatments for patients who suffer from ulcerative colitis or Crohn's disease, the two diseases known as inflammatory bowel disease (IBD). In FY 2001, the NIDDK funded about 100 projects targeted entirely or in part towards IBD. In addition, NIDDK funded three designated IBD Digestive Disease Centers that devote a significant portion of their research to IBD. In FY 2001, the NIDDK published a Request for Applications (RFA) to develop a consortium to determine the genetic basis for IBD, an RFA for additional Digestive Diseases Research Centers, an initiative to encourage development of clinical research projects, a Program Announcement for innovative and exploratory research in digestive diseases, and an RFA on gastrointestinal progenitor cells, all of which directly or indirectly encourage IBD related research. In addition, the NIDDK co-sponsored an RFA with NIAID on the use of novel approaches to identify infectious causes of chronic diseases such as Crohn's disease and ulcerative colitis.

Item

End-Stage Renal Disease – There is preliminary evidence that many end-stage renal disease patients could have improved outcomes from an increased frequency of dialysis. The Committee is pleased that NIDDK and the Centers for Medicare and Medicaid Services (CMS) hosted a planning meeting earlier this year in preparation for a jointly funded clinical trial to study the efficacy of daily dialysis. The Committee requests that the Director of the Institute be prepared to provide a progress report on this initiative at the fiscal year 2003 appropriations hearing. (p. 68)

Action Taken or to be Taken

The NIDDK convened a workshop on daily dialysis in April 2001. The participants were supportive of preliminary data that suggests the benefit of more frequent dialysis, but stressed the importance of more research to assess the value of this new therapeutic approach. The group recommended the implementation of a carefully designed randomized trial of frequent dialysis. Preliminary studies will guide development of trial strategies to determine the benefit to patients of more intensive dialysis regimens. The NIDDK and CMS are currently exploring the feasibility of arrangements that, in the context of a trial, would allow reimbursement of the additional care costs under a CMS waiver, which would be needed for the NIDDK to initiate the trial. The NIDDK has drafted a proposal that is currently under review by CMS. The Institute is also assessing the feasibility of implementing a study through the United States Renal Data System to assess outcomes of patients undergoing frequent dialysis.

Item

Glomerular Injury Research – The Committee is pleased that NIDDK is working to initiate several clinical trials related to glomerular injury and urges the Institute to enhance its efforts in this area through all available mechanisms, as appropriate, including a consensus development conference. (p. 68)

Action Taken or to be Taken

The NIDDK is expanding research on glomerular injury. The Institute and the American Society of Pediatric Nephrology jointly convened a task group in October 2000, to gather information on the criteria for, and the nature of, interventions for a clinical trial on focal segmental glomerulosclerosis (FSGS). FSGS is a kidney disease that often progresses to end-stage kidney failure and is particularly common in African-Americans. Based on recommendations from this workshop, the NIDDK issued a Request for Applications entitled “Focal Segmental Glomerulosclerosis (FSGS) in Children and Young Adults Interventional Study.” The purpose of this initiative is to support a multi-center clinical trial to examine the impact of immunomodulatory therapy on the excretion of protein in the urine – proteinuria – which is a measure of kidney function and progressive kidney disease. If successful, the results of the trial will guide physicians in providing the safest and most efficient care for children and young adults with FSGS.

In addition, the NIDDK will hold a scientific workshop on the relation of proteinuria to the progression of disease and to therapy. The workshop also will examine other potential markers for kidney disease progression, such as cystatin and TGF-beta, as well as the prospects for new molecular diagnostic screening methods.

Item

Hepatitis C – The Committee is encouraged that the HALT-Hepatitis C clinical trial is expected to yield important information about the relatively low response rates to current hepatitis C treatments. The Committee is also encouraged that ten promising ancillary research projects have been developed. The Director of the Institute should be prepared to provide a progress report of this trial at the fiscal year 2003 appropriations hearing. The Committee encourages NIDDK to enhance efforts to study the different response rates of the various racial and ethnic groups through all available mechanisms, as appropriate. The Committee also encourages NIDDK to explore ways to work with public and non-profit organizations to assist with patient accrual. The Committee is pleased to learn that a new consensus conference is scheduled for September 2002. (p. 68)

Action Taken or to be Taken

The HALT-C clinical trial is a seven year study of therapy for hepatitis C focusing on patients with advanced disease (with severe fibrosis or cirrhosis) who have not responded to conventional therapy and for whom there are no other practical options available. Patients are randomly assigned to receive long-term treatment with pegylated interferon (a once weekly injection) or no therapy. Patients will be intensively studied for both beneficial and adverse effects, supplemented by ten separately funded ancillary studies. This trial is designed to enroll over 1200 patients, with enrollment scheduled to be completed by December 2002.

Major differences in response rates to therapy of hepatitis C were first identified by NIDDK investigators. Several studies have now shown that the response rate to antiviral therapy of African American patients is two- or three-fold less than that of Caucasian and Asian patients.

The reasons for resistance to treatment are unknown. To address this issue, the NIDDK has designed a study to examine factors that might account for treatment resistance; this study is referred to as the Virahep-C Study. The intention is to administer first-time treatment to 200 Caucasians and 200 African-Americans with chronic hepatitis C and study them intensely during treatment for virological, immunological, cytokine-signalling, and host genetic differences in an effort to uncover the reasons for the poor response to treatment. The Virahep-C Study has just begun, and involves eight clinical centers, a coordinating center, and four groups of scientists who will conduct ancillary studies. At present, the Virahep-C study protocol is being developed, and a virology center will be selected in the future. NIDDK investigators will be pleased to work with public and non-profit organizations to help identify persons eligible for this study. Of extreme importance is that study participants must have received previous treatment to which they failed to respond.

An update of the Consensus Development Conference, entitled "Management of Hepatitis C: 2002," has been scheduled for June 2002. This conference promises to have a major influence on practical clinical issues of diagnosis, prevention and treatment of hepatitis C and will draw international attention. The Consensus Development Conference format allows for wide dissemination of scientifically sound, evidence-based recommendations for management, a critical need in this disease, for which diagnostic assays and treatments are so rapidly improving.

Item

Interstitial Cystitis – The Committee understands that research on interstitial cystitis (IC) is progressing and is encouraged by the recent discovery and identification of specific markers in the urine of patients with IC. This marker will not only help in selecting patients for successful therapy, but will allow the development of new, specific, targeted therapies that can cure this chronic disabling disease. The Committee encourages NIDDK to enhance research efforts in this area. The Committee also understands that NIDDK convened a Bladder Research Review Group in 2001 to create a strategic plan and set research priorities for all aspects of bladder disease, including IC, and encourages the Institute to implement this plan as expeditiously as possible. The Committee is pleased with the progress of the IC clinical trials groups and encourages NIDDK to consider its continuation. Patients with IC frequently get multiple disorders, including irritable bowel syndrome, vulvodynia, allergies, Crohn's disease, ulcerative colitis, and fibromyalgia. The Committee encourages NIDDK to support collaborative research on the etiology, diagnosis, genetics, pathophysiology and epidemiology of IC that includes urologists, neurologists, visceral pain specialists, and specialists in vulvodynia, irritable bowel syndrome and irritable bowel diseases and genetics. (p. 69)

Action Taken or to be Taken

The NIDDK is committed to continuing the momentum achieved in interstitial cystitis (IC) research. One challenge faced by clinicians and researchers is determining the extent of IC in the U.S. population. IC is particularly difficult to diagnose as it presents as a variable complex of disabling symptoms. In addition, risk factors for these complexes and their impact on quality of life are also largely unknown. The NIDDK recently funded a Request for Applications issued in July 2000, entitled "Epidemiology of Chronic Pelvic Pain of the Bladder and Interstitial Cystitis."

This study will obtain accurate epidemiological information on chronic pelvic pain of bladder origin in the U.S. population over a wide age range, in women and men, and in representative racial and ethnic groups. Previous studies of IC have focused almost entirely on highly selected populations and do not provide adequate population estimates of its burden or the impact of the more inclusive complex of chronic pelvic pain of the bladder. The results of this study should be invaluable for setting goals for IC research in conjunction with the recommendations of the Bladder Research PRG group, once their report, which is currently in final draft form, is available.

In 1999, the NIDDK began its first clinical trial testing treatments for IC. This trial is comparing two oral medications, one already FDA approved for IC treatment (pentosan polysulfate sodium) with a new one (hydroxyzine hydrochloride) for possible combined use to bring more potent relief of IC symptoms. Recently, the NIDDK began a second clinical trial. The IC Clinical Trials Group study will test whether administering the bacterium *Bacillus Calmette-Guérin* (BCG) in a bladder wash will relieve the pelvic pain and frequent urination that are hallmarks of IC. Exactly how BCG works in the bladder is still a mystery, but research suggests it may stimulate a protective immune response and downplay a harmful one in the IC bladder. The NIDDK is strongly committed to funding clinical trials on IC, and will carefully evaluate the specific scientific opportunities and clinical trial ideas that are most promising in order to determine the best mechanism of support for future trials.

There is growing recognition of the importance of medical expertise in visceral pain management in approaches to IC, and the value that treatment experience with respect to irritable bowel syndrome and other disorders may have for IC. Such collaborative research efforts to combat IC were emphasized at a two day international symposium, "Interstitial Cystitis and Bladder Research," in October 2000, co-sponsored by NIDDK and the Interstitial Cystitis Association, as well as at the Bladder Research Progress Review Group meeting in July 2001. The NIDDK is currently funding a number of studies that bring these different types of expertise to bear on IC. Such studies may result in improved therapeutic approaches for patients suffering from IC.

Item

Kidney Disease – The yearly mortality rate for dialysis patients is approximately 20 percent and it is estimated that the renal failure population will double over the next 10 years. The Committee urges NIDDK to enhance kidney disease research through all available mechanisms, as appropriate, including clinical trials. The Committee requests that the Director of the Institute be prepared to give a progress report at the fiscal year 2003 appropriations hearing. (p. 69)

Action Taken or to be Taken

The NIDDK has funded and continues to fund a wide range of research efforts into kidney disease, including a number of clinical trials. Examples include the following:

The recently-completed African American Study of Kidney Disease and Hypertension (AASK) found that people with kidney disease and protein in their urine were more likely to postpone kidney failure using either an angiotensin-converting enzyme inhibitor or a beta blocker than a

calcium channel blocker. To follow up on this finding, the NIDDK will investigate the environmental, socio-economic, genetic, physiologic, and other co-morbid factors that influence progression of kidney disease as part of the AASK Continuation Study.

Also, the NIDDK plans to initiate the Chronic Renal Insufficiency Cohort (CRIC) study by mid-to-late 2002. CRIC will be a longitudinal prospective study of patients with mild-to-moderate renal insufficiency. The study is designed to determine the risk factors for rapid decline in renal function and development of cardiovascular disease.

A very sizeable body of correlative data suggests that elevation of homocysteine levels causes premature atherosclerotic disease; however, data supporting the inference that lowering homocysteine will reduce risk is sparse. Because patients with renal insufficiency demonstrate both elevated homocysteine levels and markedly enhanced cardiovascular disease risk, the NIDDK will conduct a clinical trial (FAVORIT) to determine whether lowering homocysteine levels with folate and B vitamin supplementation reduces mortality in renal transplant patients.

The NIDDK is also planning to establish a research network to design and implement clinical trials to slow the progressive loss of renal function in Polycystic Kidney Disease (PKD). It is envisioned that the network will develop and execute both pilot and feasibility trials and a large, randomized, controlled clinical trial on blockade of the renin-angiotensin axis in patients with PKD. The Institute also plans to create a network to test the value of selected immunosuppressive interventions with converting enzyme inhibitors as an adjuvant intervention for preventing progression of focal segmental glomerulosclerosis in children and young adults.

Item

Liver Disease – The Committee is pleased with the research focus on hepatitis C, but urges the Institute to continue focus on other liver diseases, hepatocellular carcinoma in collaboration with NCI, alcoholic liver disease in collaboration with NIAAA, and hereditary hemochromatosis in collaboration with NHLBI. The Committee is aware that NIDDK, working with NCCAM, has begun studies of some complementary and alternative medicine treatments for liver diseases. The Committee urges NIDDK to continue to support this research and to assure that the public is aware of the results. (p. 69)

Action Taken or to be Taken

The NIDDK has initiated a large-scale clinical trial in hepatitis C, studying long-term treatment of HCV-infected persons who have not responded to optimal standard therapy. The trial will continue for seven years with major co-support from NCI, NIAID, NCMHD and industry. Ancillary studies have been developed to complement the trial. These studies will focus on non-invasive assessment of liver fibrosis; early detection of liver cancer; the viral and immune factors that lead to worsening of hepatitis C; the usefulness of new virological tests for hepatitis C; and how best to manage long-term therapy of this disease. The Institute is also participating in a major surveillance study on hemochromatosis being supported by the NHLBI, and, in response to a FY 1999 initiative co-sponsored with NHLBI, has funded several research projects that emphasize the mechanisms leading to hemochromatosis and the prevention and treatment of iron

overload. An Adult-to-Adult Living Donor Liver Transplantation Cohort Study is planned for funding in FY 2002 and will include studies of alcoholic liver disease and liver cancer. Similarly, a Non-Alcoholic Steatohepatitis (NASH) Network is planned for funding in FY 2002. Its focus will be fatty liver disease, which has major implications for elucidating the cause of alcoholic liver disease. NASH is a liver disease that is similar to alcoholic liver disease but occurs in people who do not drink alcohol excessively. Its cause is unknown, but it may have the same pathogenesis as alcoholic liver disease. The NCI is beginning a Progress Review Group in liver cancer; the NIDDK will work with this program, which will help to define research needs.

In August 1999, NIDDK and NCCAM co-sponsored a symposium, "Complementary and Alternative Medicine in Chronic Liver Disease." As a result of this meeting, silymarin (milk thistle) was identified as a high priority for further study. The NIDDK recently co-sponsored a Request for Applications with NCCAM, soliciting Small Business Innovative Research Grants to develop a standardized preparation of silymarin (milk thistle) of sufficient quality and purity to use in clinical trials. A grant was awarded for the production of silymarin, as well as for the development of assays to measure silymarin levels in serum to allow for pharmacokinetic studies of silymarin that would permit appropriate choice of dose and frequency of administration (once, twice or three times a day). Once pharmacologically active and pure silymarin has been prepared and preliminary studies identify the optimal dose and regimen of treatment, it will be possible to design and perform full scale randomized controlled trials. The major conditions that will be focused upon for evaluation of silymarin will be hepatitis C, hepatitis B, non-alcoholic steatohepatitis (fatty liver disease), and alcoholic liver disease.

The National Digestive Diseases Information Clearinghouse (NDDIC) disseminates information on digestive diseases. Working closely with professional, patient, and voluntary associations, government agencies, and other organizations, the NDDIC will continue to identify and respond to information needs about digestive diseases.

Item

Living Donor Liver Transplantation – The Committee is encouraged by the growing number of transplants using living donors who contribute a portion of their liver to a recipient. The Committee urges NIDDK to enhance research to study the outcome of both donors and recipients, define optimal surgical procedures, and identify eligibility criteria in order to increase living donor transplantations through all available mechanisms, as appropriate, including the establishment of clinical centers and a data coordinating center. (p. 69)

Action Taken or to be Taken

In December 2000, the NIDDK, in collaboration with NIAID, the Association for the Study of Liver Diseases, and the American Society of Transplant Surgeons, sponsored a clinical workshop on living donor liver transplantation (LDLT). In response to that meeting, the NIDDK issued a Request for Applications (RFA) in July 2001, inviting cooperative agreement applications for clinical and coordinating centers to conduct a LDLT Cohort Study among adults awaiting transplantation. The goal of this RFA is to select one Data Coordinating Center and as many as 8 Transplantation Centers to participate in planning and implementing a multi-center study on adult

LDLT. This type of coordinating mechanism is necessary, as adult-to-adult LDLT is a relatively new procedure and few cases are performed at any one center. Current approaches to the patient and donor are too diverse to provide reliable information on outcomes from individual centers. This RFA will support the establishment and maintenance of the infrastructure required to accrue and follow sufficient numbers of patients being considered for and undergoing LDLT.

The primary research objectives of the proposed LDLT Cohort Study concern factors that influence the outcomes of adult-to-adult LDLT. Particular questions that may be addressed by this study include: how the outcomes of LDLT compare with those of cadaveric transplantation; what the immediate and long term risks are for the donor; how LDLT affects the donor's quality of life, including financial and psycho-social effects; how the size and condition of the donor organ affect outcomes; what operative procedures produce optimal outcomes; whether costs differ substantially between LDLT and cadaveric transplantation; how LDLT affects disease recurrence in the recipient; and how pre-operative preparation can be optimized to prevent disease recurrence, rejection and other morbidity. The study funded through this RFA should be capable of recruiting sufficient patient and donor pairs to answer these and other critical research questions regarding the effectiveness of adult-to-adult LDLT.

Item

Mucopolysaccharidosis Diseases – The Committee encourages NIDDK to enhance research efforts in the development of effective treatments for mucopolysaccharidosis (MPS) disorders through all available mechanisms, as appropriate, including genotype-phenotype studies, cell biology and the pathophysiology of brain damage and substrate deprivation as it relates to MPS disorders. The Committee also encourages NIDDK, NINDS and NICHD to collaborate its research efforts and enhance support for both current MPS studies as well as new efforts to develop effective therapies. (pp. 69-70)

Action Taken or to be Taken

The NIDDK, as well as NINDS and NICHD, supports both basic research into the underlying biological causes of MPS, as well as animal studies into novel approaches to the treatment of MPS. Research efforts include studies of enzyme replacement therapy and a number of therapeutic approaches using gene transfer techniques. The NIDDK also supports research into genetic metabolic diseases through Small Business Innovation Research grants. The Institute has joined NINDS and other institutes on an initiative entitled, "Gene Therapy for Neurological Disorders." It is expected that scientifically meritorious applications received in response to this initiative will be funded in FY 2002. The NIH will continue to partner with the National MPS Society to identify the optimal means to promote and stimulate research. A workshop entitled "New Therapeutics in Skeletal and Central Nervous Systems: Applications to Mucopolysaccharidosis," is planned for September 2002. This workshop will be sponsored by NINDS and co-sponsored by NIDDK, NICHD, and the NIH Office of Rare Diseases (NIH ORD). Using MPS as a model, workshop attendees will discuss the barriers to delivering therapies to the nervous system, and will explore options to overcoming these obstacles. Both this workshop and the initiative on gene therapy for neurological disorders were developed following an October 2000 meeting on gene therapy, which was sponsored by NINDS and the NIH ORD.

Item

Pediatric Kidney Disease – The Committee remains concerned over the alarming number of children and adolescents suffering from kidney disease, a disproportionate number of whom are minorities. Chronic kidney failure among young people results in particularly severe consequences. Normal growth and development are impaired, and many scientists believe that chronic kidney failure has a profound effect on the developing brain, often resulting in learning disabilities and mental retardation. Research and treatment are hampered by the critical and growing shortage of pediatric kidney specialists, individuals who are specially trained and qualified to manage renal disease that arise in this vulnerable age group. The Committee urges NIDDK to enhance research on both congenital and acquired chronic renal failure through all available mechanisms, as appropriate, including the molecular mechanisms underlying growth failure in children with kidney failure, hypertension as a risk factor for cardiovascular and renal disease, and the development of a database of genetic renal diseases. NIDDK is also encouraged to consider launching new training initiatives to help ease the workforce shortage in this field. (p. 70)

Action Taken or to be Taken

The NIDDK has sought to encourage research on normal kidney development and on pediatric kidney disease. Ongoing initiatives include studies on diabetic and non-diabetic nephropathy susceptibility genes, a medical imaging study to assess progression of polycystic kidney disease, and the establishment of four Interdisciplinary Centers for Polycystic Kidney Disease Research.

New efforts include a clinical trial, to be funded within the next year, to examine the impact of immunomodulatory therapy on an important kidney disease of children, focal segmental glomerulosclerosis (FSGS). If successful, the results of the clinical trial will guide physicians in providing the safest and most efficient care for children and young adults with FSGS.

The Institute is planning to establish a task force to determine the most important issues to address in longitudinal epidemiologic studies in the pediatric population. A group of pediatric nephrologists and epidemiologists will meet this Spring to review issues about growth and development and risk factors for future diseases in the pediatric population that need to be examined in longitudinal studies. The task force will assist the NIDDK in defining the most important issues.

In addition, the NIDDK is committed to issuing a Request for Proposals for a registry for selected genetic diseases that cause kidney failure in children. This initiative, entitled “Database and Registry for Genetic Renal and Genitourinary Diseases,” emanated from the Strategic Plan for Research Needs in Pediatric Kidney Disease developed by an NIDDK-American Society of

Pediatric Nephrology task force. The program would create a registry of well-characterized pediatric nephrology and urology patients with single-gene disorders that can be accessed by qualified investigators for approved basic and clinical studies.

The NIDDK will continue to expand research on pediatric kidney diseases based on recent and emerging scientific opportunities, and will of course consider the recommendations contained in the Strategic Plan in developing future program initiatives in pediatric nephrology.

The NIDDK is aware that pediatric nephrology is a field where there is a critical manpower shortage. The Institute is working through the existing mechanisms – both the Loan Repayment Program and the research training grant mechanism – to provide support for research training in this area.

Item

Pediatric Liver Disease – Biliary atresia is the most common cause of liver transplantation in children. The Committee urges NIDDK to enhance efforts to address this and other pediatric liver diseases through all available mechanisms, as appropriate including the establishment of clinical centers and a data-coordinating center. (p. 70)

Action Taken or to be Taken

The NIDDK intends to further research on biliary atresia with a planned initiative to establish a Clinical Research Consortium. The consortium will facilitate clinical, epidemiological, and therapeutic research in biliary atresia and idiopathic neonatal hepatitis, two important and rare pediatric liver diseases. The consortium will consist of about eight-to-ten pediatric clinical research centers and a data-coordinating center. Two other new NIDDK initiatives encompass in scope pediatric liver diseases, among other digestive diseases: one will support small clinical research grants in digestive diseases and nutrition, and the other will support innovative and exploratory research in digestive diseases and nutrition.

Item

Polycystic Kidney Disease – The Committee is encouraged that the number of research discoveries aimed at treatment and a cure for Polycystic Kidney Disease (PKD) are numerous.... In light of the scientific momentum in this field, the Committee urges the Institute to continue to implement the PKD strategic plan through all available mechanisms, as appropriate. (p. 70)

Action Taken or to be Taken

The NIDDK's funding for PKD research has nearly tripled over the past 5 years. In expanding its PKD research portfolio, the NIDDK has made substantial progress in implementing the PKD Strategic Plan, a report developed at the November 1998 Strategic Planning Conference for PKD Research. The report recommended three opportunities for expansion of NIH PKD research. By the end of FY 2001, the NIDDK had developed, implemented, and expanded two major research initiatives addressing recommendations in the report. First, in FY 1999, the Institute issued a Request for Applications (RFA) to encourage development of state-of-the-art imaging methods for PKD. The primary goal of this initiative is to test whether imaging techniques can provide sufficiently accurate and reproducible markers of progression of renal disease in PKD to permit their use in clinical trials. Under the umbrella Consortium for Radiologic Imaging Studies of

Polycystic Kidney Disease (CRISP) study, the NIDDK funded the Data Coordinating and Imaging Analysis Center and, in FY 2000, funded three Participating Clinical Centers. In FY 2001, the NIDDK expanded the CRISP study to include ultrasound imaging methods and increased investment in image processing algorithms.

The second program initiative established four Specialized Centers for Polycystic Kidney Disease Research in FY 1999. These centers are expanding the basic research infrastructure in PKD. The studies should foster and extend the development of new approaches into the causes, early diagnosis, and improved treatments for PKD. An example of the insights emerging from these centers is the recent finding that an inhibitor of tyrosine kinase (an enzyme) can stop cyst formation in a mouse PKD model. The products of this research should facilitate the pace at which clinical studies can evolve.

In FY 2002, the NIDDK plans to bolster its support of research on PKD treatment by implementing a multi-center interventional clinical trial to assess the best strategy for reducing morbidity and mortality in PKD. An RFA was issued in May 2001. The main issues to be addressed are the optimum target levels for blood pressure control, and whether angiotensin-converting enzyme inhibitors offer superior benefit over other anti-hypertensive agents in slowing the progression of PKD. In addition, proposals for pilot and feasibility studies for tests of new therapies have been invited.

Item

Prostatitis – The Committee...encourages NIDDK to enhance research in areas that will correlate clinical findings with fundamental research studies. (pp. 70-71)

Action Taken or to be Taken

The NIDDK's prostatitis research program has grown substantially, increasing nearly three-fold between FY 1997 and FY 2001. The program includes both clinical and basic research addressing questions about diagnosis, prognosis, cause and treatment of this terrible problem. At the forefront of clinical research is NIDDK's Chronic Prostatitis Collaborative Research Network (CPCRN), which has already developed and validated a questionnaire being used by the wider research community to assess accurately symptom severity and quality of life. The network is documenting symptoms, possible risk factors, medical histories, treatments, and the results of blood, prostate fluid, semen, and urine tests. The CPCRN recently began its first clinical study comparing tamsulosin hydrochloride, which may increase the flow of urine and decrease pelvic pain, and the antibiotic ciprofloxacin, which may reduce inflammation, with placebo. Two new clinical sites were added in FY 2001 to help recruit patients, especially minorities, and in FY 2002, NIDDK will extend funding for the CPCRN for an additional year so that centers may plan and conduct more clinical trials.

A recent NIDDK initiative will expand the pool of prostate researchers and increase the use of novel technologies and innovative approaches in prostate research as part of the Institute's Prostate Research Novel Exploratory Teams (Prostate Research NET). This action is the result of several information-gathering and planning meetings: the NCI-sponsored Prostate Research

Progress Review Group, April 1997; the International Symposium on Prostate Growth, March 1998; and the Symposium on Prostate Growth and Aging, September 2000.

Item

Urinary Incontinence – Urinary incontinence afflicts approximately 13 million adults in the United States, 85 percent of whom are women. The Committee encourages NIDDK to enhance research in this area through all available mechanisms, as appropriate including support to the urinary incontinence treatment network and clinical trials. (p. 71)

Action Taken or to be Taken

The Bladder Research Progress Review Group (Bladder PRG) met in July 2001, to evaluate the bladder research portfolios of NIDDK and NIH, identify research opportunities, and define unmet needs in bladder research. The report containing the Bladder PRG's recommendations is currently being developed by the steering committee. The NIDDK expects that the report will be an invaluable guide for targeting future research efforts in many areas, including urinary incontinence.

The NIDDK, in collaboration with NICHD, is currently supporting research on urinary incontinence through the Urinary Incontinence Treatment Network Initiative. This is a multi-center consortium of investigators supported by a cooperative agreement. It originally included four vanguard Continence Treatment Centers and a single Biostatistical Coordinating Center. The primary objective of the Network is to evaluate the long-term outcomes of the most commonly applied treatments for women with the diagnoses of stress and mixed urinary incontinence. This much-needed assessment will provide both physicians and patients with information necessary to make well-informed decisions about the best treatment options. To increase the number of patients enrolled and to enhance the ethnic and racial diversity of the study population, the NIDDK added five Continence Treatment Centers to the Network in FY 2001. The new awardees will participate in a 4 year prospective cohort study of women who have undergone different surgical procedures for urinary incontinence. This study will use protocols developed through the collaborative efforts of the original centers and the NIDDK and NICHD.

National Institute of Diabetes and Digestive and Kidney Diseases
SIGNIFICANT ITEMS IN HOUSE AND SENATE APPROPRIATIONS
COMMITTEE REPORTS

FY 2002 Senate Appropriations Committee Report Language (S. Rpt. 107-84)

Item

Adult Stem Cell Research – The Committee is aware of the rapidly developing field of research in adult stem cell plasticity, and it encourages NIDDK to work with the American Society of Hematology in determining the next steps for realizing the full potential of adult stem cell biology in curing disease. The Committee encourages the National Institutes of Health to continue working with the Office of Naval Research to support research to develop curative therapies for patients with breast cancer, leukemia, lymphoma, and sickle cell disease, and for victims of radiation, chemical, and biological exposure. (p. 130)

Action Taken or to be Taken

Because of the reported potential for adult hematopoietic stem cells to give rise to non-hematopoietic tissues as well as cells of the hematopoietic lineage, in November 2000, along with the NHLBI and the NINDS, the NIDDK announced a Request for Applications (RFA) entitled “Stem Cell Plasticity in Hematopoietic and Non-hematopoietic Tissue.” This research solicitation was intended to promote the thorough exploration and characterization of stem cell plasticity in hematopoietic and non-hematopoietic tissue. In October 2001, NIDDK announced a related RFA, “Hematopoietic Cell Lineage Genome Anatomy Projects,” which is intended to develop the necessary biological procedures and reagents for characterization of cells of the hematopoietic lineage and to characterize gene expression patterns in these cells using advanced technologies and bioinformatics techniques.

In addition to these efforts, the Trans-NIDDK Stem Cell and Developmental Biology Strategic Planning Group recently drafted a set of recommendations for stimulating research in this area. The NIDDK plans to create a consortium of investigators, which will include one of the past presidents of the American Society for Hematology, to provide a comprehensive delineation of the patterns of gene expression during hematopoietic differentiation.

While the NIH is no longer working directly with the Office of Naval Research, research projects to develop curative therapies for patients with breast cancer, leukemia, lymphoma, and sickle cell disease, and for victims of radiation, chemical, and biological exposure, have been incorporated into the intramural research programs of the NIDDK, the NCI, and other NIH institutes.

Item

Bladder Disease – ...The Committee is also pleased by NIDDK's issuance of an RFA related to urinary incontinence. While these steps are important, the Committee remains concerned about the funding level for research in bladder disease. The Committee urges the Institute to finalize a long-term research strategy based upon the recommendations of the Bladder Research Progress Review Group convened in 2001. The Committee supports increased bladder disease research by any available means, and encourages the Institute to consider initiating and maintaining a National Cell/Tissue Archive for Bladder Disease. (p. 131)

Action Taken or to be Taken

Please refer to pages 37 & 38 of this document (House item: "Bladder Disease") for NIDDK's response to this significant item regarding "Bladder Disease."

Item

Complementary and Alternative Medicine Treatments – Complementary and alternative medicine treatments for liver diseases are becoming more common despite limited evidence of safety and efficacy. The Committee is aware that the NIDDK, working with the NCCAM, has begun funding studies of some of these treatments. The Committee urges the NIDDK to continue supporting this research and ensure that the public is aware of the results. (p. 131)

Action Taken or to be Taken

Please refer to pages 47 & 48 of this document (House item: "Liver Disease") for NIDDK's response to this significant item regarding "Complementary and Alternative Medicine Treatments."

Item

Congenital Urological Disorders – ...The Committee urges NIDDK to collaborate with other interested institutes in developing a strategic research plan to address congenital urological disorders in the pediatric age group, and to initiate new, innovative research projects in areas such as ureteral reflux, fetal hydronephrosis, and bladder dysfunction of spina bifida. (p. 131)

Action Taken or to be Taken

The NIDDK is planning a scientific workshop for 2002 on neonatal obstructive uropathy. Working together with the American Society of Pediatric Nephrology and the pediatric urology subgroup of the American Urological Association, the NIDDK expects to receive recommendations for areas of research on congenital urological disorders that should be pursued in the future. The NIDDK will seek and encourage collaboration with other institutes and centers of the NIH in the sponsorship and planning of this workshop and in the implementation of plans for research that derive from the workshop.

Item

Diabetes in Native Hawaiians – The Committee recognizes the Institute's interest in studying the incidence of diabetes in native American, Hawaiian, and Alaskan populations, and encourages NIDDK to include native Hawaiian and Alaskan populations, the Mississippi Band of the Choctaw Indians, and the Eastern Band of the Cherokee Indians in diabetes studies. (p. 131)

Action Taken or to be Taken

The NIDDK supports many research efforts aimed at understanding, treating, and preventing type 2 diabetes in native American, Hawaiian, and Alaskan populations. Examples include the following:

The Diabetes Prevention Program (DPP) is the first major clinical trial to show that diet and exercise can effectively delay diabetes in a diverse American population of overweight people with impaired glucose tolerance, a condition in which blood sugar levels are higher than normal but not yet diabetic. Participants randomly assigned to lifestyle intervention reduced their risk of getting type 2 diabetes by 58 percent. The DPP enrolled over 3,200 participants, 45 percent of whom were from minority groups that suffer disproportionately from type 2 diabetes, including African Americans, Hispanic Americans, Asian Americans and Pacific Islanders, and American Indians. Among the 27 clinical centers that participated in the DPP, the University of Washington, through a contract with the University of Hawaii, made a special effort to include Native Hawaiians. Sixty-four individuals from Hawaii participated in the DPP.

The NIDDK is also supporting an epidemiologic study to evaluate potential risk factors for type 2 diabetes and cardiovascular disease among members of the Cherokee Nation of Oklahoma. The Cherokee Nation was selected as the study population because of its high prevalence of diabetes, varying degree of Indian blood, large membership, excellent health care facilities, and strong interest in research among the tribal leaders and health care professionals. The cohort for this study will consist of individuals from a wide range of ages and varying degrees of Indian blood. Investigators plan to analyze a number of potential risk factors for type 2 diabetes and cardiovascular disease in this cohort, including family history of diabetes, degree of Indian blood, obesity, diet, physical activity, and social and economic factors.

A major, randomized clinical trial initiated by the NIDDK is “Look AHEAD: Action for Health in Diabetes,” which is co-sponsored by NHLBI, NIEHS, NINR, NCMHD, the NIH Office of Research on Women’s Health, and the Centers for Disease Control and Prevention (CDC). This clinical trial is studying whether interventions designed to produce sustained weight loss in obese individuals with type 2 diabetes improve health. The trial is expected to enroll 5,000 participants from a wide range of minority populations with varying ethnic/racial backgrounds, in order to reflect the disproportionate impact of diabetes in these groups. In addition to 15 clinical centers and a data-coordinating center, a Southwest American Indian Look AHEAD clinical center has been formed at the NIDDK Phoenix Epidemiology and Clinical Research Branch in Arizona. Look AHEAD is also intended to serve as a resource for basic research studies relating to obesity, a major risk factor for the development of type 2 diabetes.

Type 2 diabetes in children is an emerging problem in communities throughout the U.S. The magnitude of the problem in minority communities, and especially in Native Americans and Alaskan Natives, reflects the higher incidence rates of diabetes in these groups compared to the general population. An NIDDK research initiative, co-sponsored by the NICHD, on “Type 2 Diabetes in the Pediatric Population,” will further research leading to a new understanding of why diabetes is increasingly occurring at younger ages in minority populations and will encourage new approaches to prevent and treat type 2 diabetes in at-risk children. Research supported through this solicitation includes diagnostic landmarks in the development of type 2 diabetes; school-based interventions; pathophysiology of type 2 diabetes in youth, adolescents, and teens; and screening for genes predisposing to type 2 diabetes in the pediatric population. In addition, the NIDDK plans to initiate clinical trials for the primary prevention and treatment of type 2 diabetes in children. Primary prevention trials will focus on cost-effective, school- or community-based interventions with the potential for broad, population-wide application. Treatment trials may include lifestyle changes and/or pharmacologic therapy.

Several research groups supported by the NIDDK are actively searching for genes for type 2 diabetes in minority populations, including Mexican Americans and Native Americans. They have found that certain genes appear to make a contribution to susceptibility to type 2 diabetes in Mexican Americans. In Pima Indians, studies show that a certain repeated genetic sequence is more common in individuals with onset of type 2 diabetes at an early age. Understanding the genes that determine type 2 diabetes in these populations will lead to a more complete knowledge of the disease process in other minority populations, including other Native American populations.

The NIDDK has recently issued an announcement to encourage research on the translation of recent advances in the prevention and treatment of type 2 diabetes into clinical practice for individuals and communities at-risk. Of particular interest are interventions that focus on translating new advances into practice in under-served and minority populations.

The NIDDK and the CDC are jointly sponsoring the National Diabetes Education Program (NDEP). Its goal is to reduce the death and disability associated with diabetes and its complications. Special efforts are being made to address the needs of ethnic groups that are hardest hit by diabetes, including Alaska Natives, Native Americans, Asian and Pacific Islanders, and Hispanic Americans. Through these efforts, the NDEP hopes to improve the treatment and health outcomes for people with diabetes, promote early diagnosis, and ultimately, prevent the onset of diabetes.

Item

Diabetic Macular Edema – The Committee urges the Director of NIDDK to consider the National Eye Institute's new multicenter clinical trial initiative on diabetic macular edema, a major cause of visual loss in patients with diabetes, when allocating the special funds targeted for diabetes made available to the Department. (p. 132)

Action Taken or to be Taken

On April 12, 2000, the NIDDK convened a panel of leading diabetes researchers to advise the Department of Health and Human Services on opportunities for research funding with the special type 1 diabetes funds. The advisory committee noted that several promising new drugs are under development to prevent retinopathy and other microvascular complications. Also, some surrogate outcomes have recently been developed which can be used for short-term pilot studies to prevent retinopathy. The panel of advisors recommended support of pilot studies of promising agents to aid in the transition from the bench to clinical investigation. A research solicitation was issued to create a diabetic macular edema clinical research network for support of clinical trials. It is anticipated that \$2 million per year will be provided from the special type 1 diabetes funds for this purpose in FY 2002 and FY 2003. In addition, another \$2 million per year from the special diabetes funds has been allocated for a solicitation jointly issued by the NIDDK, the NEI and the NINDS to develop biomarkers that could be used as outcome measures in clinical trials testing new therapeutic agents for the eye, kidney and nerve complications of diabetes.

Item

Digestive Cancers – The Committee is pleased with the NCI Progress Review Group on Pancreatic Cancer and urges the NIDDK to collaborate with NCI on mutual research areas and awareness programs for the scientific and lay communities. The Committee urges NIDDK to establish translational research activities to understand the inter-relationships of pancreatitis, diabetes, and pancreatic cancer. (p. 132)

Action Taken or to be Taken

The NIDDK supports research on all aspects of pancreatic development, including studies on beta cell development with a focus on diabetes. The Institute recently sponsored a meeting on “Pancreatic Development, Proliferation and Stem Cells” with the American Diabetes Association and Juvenile Diabetes Research Foundation International. The objective of the two-day workshop was to bring together investigators from multiple disciplines conducting state-of-the-art research in developmental biology of the pancreas, islet cell biology and stem cells. NIDDK research activities in the area of translational research include support of a Beta Cell Biology Consortium that is developing mouse models and reagents useful for understanding normal pancreatic lineage and the regulation of pancreatic gene expression, and for facilitating the identity, characterization and purification of potential pancreatic stem/progenitor cell populations. These research resources will be invaluable in understanding the origin of pancreatic ductal adenocarcinoma and in allowing a complete analysis of pancreatic tumor biology. The genomics effort directed at islets involves identifying all genes expressed at various developmental stages of islets. Many of these early precursors of the islet are also precursors of the pancreatic ductal cells from which most cancers arise. The adult pancreas is characterized by developmental plasticity in which acinar, ductal and islet lineages are capable of abnormal change in the adult cells. This observed plasticity raises considerable uncertainty regarding the true cell of origin for pancreatic ductal adenocarcinoma, but it is likely that these pancreatic cell types derive from a common epithelial precursor population during embryonic development.

The NIDDK met with the pancreas research community in March 2000 and discussed approaches to advancing research in the areas of pancreatitis and pancreatic cancer. This meeting and subsequent interactions with the community has led to several initiatives focusing on pancreas research. In June 2000, the NIDDK published a Program Announcement soliciting innovative developmental research grants (R21s) focusing on several areas in digestive diseases, but prominently upon pancreatitis and pancreas research. In October 2001, a Request for Applications was published for genome anatomy projects for progenitor cells specifically of the gastrointestinal tract, pancreas and liver. In September 2001, as a part of a large ongoing initiative in developmental biology, the NIDDK awarded three grants on the development of the pancreas and pancreatic progenitor stem cells. In November 2001, members of NIDDK staff met with the American Pancreatic Association (APA) to discuss a research agenda in the area of pancreas research. The NIDDK has stressed the need to attract new investigators into this field and will work with the APA to increase research training and career development in pancreas research.

Item

Digestive Diseases – The Committee recognizes the success of NIDDK’s Digestive Disease Centers program in addressing a wide range of disorders that result in tremendous human suffering and economic cost. The Committee continues to encourage NIDDK to expand this important program with an increased emphasis on inflammatory bowel disease. (p. 132)

Action Taken or to be Taken

Please refer to pages 42 & 43 of this document [House item: “Digestive Diseases (IBD)”] for NIDDK’s response to this significant item regarding “Digestive Diseases.”

Item

Drug-induced Liver Disease – ...The Committee urges the NIDDK, in cooperation with other appropriate Institutes and the pharmaceutical industry, to establish a national surveillance system to further document hepatotoxicity of medications and to fund research to prevent and treat this serious cause of liver injury. (p. 132)

Action Taken or to be Taken

The NIDDK sponsored a 2 day workshop on Drug-Induced Liver Disease in November 2000. The results of that meeting included the following recommendation: “A rigorous, multi-center, active and prospective database on drug-related hepatotoxicity would help promote basic research on hepatotoxicity and would be particularly useful in the development of pharmacogenomics, i.e., the role of inherited factors in rare types of reactions.” Accordingly, the NIDDK is preparing a Request for Applications (RFA) to establish a Hepatotoxicity Network, to include several clinical centers to develop criteria for the diagnosis of drug-induced liver disease and prospectively collect well-defined cases and appropriate serum, DNA, and tissue samples for analysis. This clinical network would work directly with more basic efforts in pharmacogenomics and research on drug-induced liver cell injury to help define the multiple causes of drug-induced liver disease

and clinically relevant means of prevention and treatment. This concept for an RFA will be reviewed at the time of the February 2002 NIDDK National Advisory Council meeting by the trans-NIDDK Working Group on Disease Prevention and Management. The proposal will then be finalized and the announcement directed to planned FY 2003 funding of the network. It is expected that these initiatives will be pursued in collaboration with NIEHS and NIGMS, which are currently supporting initiatives in basic pharmacogenomics.

Item

Glomerular Injury Research – The Committee urges NIDDK to expand its research efforts on glomerular injury, a group of diseases which affect the filtering mechanisms of the kidney. The Committee is pleased that in addition to basic research being conducted, NIDDK is working to initiate several clinical trials related to glomerular injury. Further, the Committee encourages NIDDK to consider initiating a consensus development conference on glomerular injury research, and to explore support for gathering prevalence data on glomerular injury. (p. 132)

Action Taken or to be Taken

Please refer to pages 43 & 44 of this document (House item: “Glomerular Injury Research”) for NIDDK’s response to this significant item regarding “Glomerular Injury Research.”

Item

Hepatitis C in African Americans – The Committee is also aware that the prevalence of hepatitis C in African Americans is more than two times greater than in Caucasians and that African Americans have a poor response rate to treatments. The Committee encourages the Institute to establish the appropriate number of clinical trial centers and a data-coordinating center to study the impact of the hepatitis C virus infection and the variable response to treatment in different human hosts. The Committee also urges the Institute to collaborate with the National Center on Minority Health and Health Disparities on this issue. (p. 133)

Action Taken or to be Taken

In December 1999, a workshop on hepatitis C in African-Americans was held at the NIH in response to reports that African-Americans have a higher prevalence of hepatitis C (HCV) than Caucasian-Americans and a lower response to treatment with interferon with or without ribavirin. The workshop – sponsored by NIDDK, NCI, NIDA, NIAID, and the Office of Research on Minority Health – reviewed current information on the prevalence, clinical course, and therapy of hepatitis C among African-Americans and explored factors that could determine different responses to treatment. In FY 2001, the NIDDK, with support from NCMHD, funded an initiative entitled, “Study of Viral Resistance to Antiviral Therapy of Chronic Hepatitis C (VIRAHEP-C): Clinical Centers, Data Coordinating Center, Ancillary Studies.” This initiative will explore the discrepancies in viral resistance to antiviral treatment. The study will include approximately 400 patients infected with HCV genotype 1, the strain of virus that is linked to viral resistance. Half of the patients will be African Americans and half will be Caucasians. The study has eight geographically distributed clinical centers and one data coordinating center and

will be complemented by three to four ancillary studies on the biological basis of antiviral resistance of hepatitis C. The focus of the study will be to define precisely the differences in response rate between African Americans and Caucasians and to elucidate the underlying causes of these differences and possible means of increasing the response rates to therapy among African Americans with hepatitis C.

Item

Hereditary Hemochromatosis – Hereditary hemochromatosis, the most common genetic disease in human beings, is associated with identified genetic mutations in 70 to 90 percent of cases. The Committee urges the Institute, working with NHLBI, to expand research funding on this common disease with particular emphasis on screening, early diagnosis, and the still-unknown genetic mutations that cause 10 to 30 percent of cases. (p. 133)

Action Taken or to be Taken

Following the cloning of the hereditary hemochromatosis (*HFE*) gene in 1996, the scientific community urged that research be supported on the advisability of screening individuals who may be at risk for hemochromatosis. Since 1998, the NIDDK has supported a large clinical study in which 41,000 individuals to date have been screened for the two most common *HFE* mutations. The most recent data from this study has revealed that, although 80 percent of individuals with hereditary hemochromatosis harbor one or both of these mutations, the mutations are necessary but not sufficient by themselves to cause fully developed hemochromatosis. Surprisingly, less than one percent of individuals carrying mutations in both copies of the *HFE* gene actually develop clinical hemochromatosis. Therefore, it is apparent that the cost of wide-scale screening for individuals with *HFE* mutations would be far beyond that first anticipated. Funding has recently been extended to explore the hypothesis that, while individuals with both mutations may be more susceptible to cardiovascular disease and other disorders, they benefit by being less susceptible to iron deficiency anemia. This phase of the study will look for additional, less common mutations that also may contribute to the incidence of hemochromatosis.

In 1999, the NIDDK and NHLBI co-sponsored an initiative entitled, “Biology of Iron Overload and New Approaches to Therapy.” This initiative supported research into the biological consequences of iron overload and towards the improvement of methods of therapy, with an emphasis on elucidating the control of iron transport and metabolism. Several research projects funded under this initiative emphasize the mechanisms leading to hemochromatosis and the prevention and treatment of iron overload. In 2001, the NIDDK, with partial support from the NIH Office of Rare Diseases, held a workshop on the noninvasive measurement of iron. The purpose of the workshop was to discuss issues involved in non-invasive iron measurement and to assist the NIDDK in designing the most effective approaches to improve such measurements. Subsequently, a grant was awarded to develop a new generation of instruments to measure body iron magnetically, and other initiatives are planned to adapt magnetic resonance imaging (MRI) to the measurement of body iron.

Item

Inflammatory Bowel Disease – The Committee has been encouraged in recent years by discoveries related to Crohn’s disease and ulcerative colitis, collectively known as inflammatory bowel disease (IBD)....The Committee believes that NIDDK should review the current intestinal transplantation procedures and make future recommendations on how they could be improved. It also encourages the Institute to implement a long-range research agenda to adequately fund research into the cause of and a cure for IBD and short bowel syndrome. (p. 133)

Action Taken or to be Taken

The NIDDK continues to maintain IBD as a high priority area for basic and clinical research aimed at discovering the causes and better treatments for patients who suffer from ulcerative colitis or Crohn’s disease. In FY 2001, NIDDK funded about 100 projects focused entirely or in part on IBD. In addition, the NIDDK funded three designated IBD Digestive Disease Centers that devote a significant portion of their research to IBD. In FY 2001, NIDDK published a Request for Applications (RFA) to develop a consortium to determine the genetic basis for IBD, an RFA for additional Digestive Diseases Research Centers, an initiative to encourage development of clinical research projects, a Program Announcement for innovative and exploratory research in digestive diseases, and an RFA on gastrointestinal progenitor cells, all of which directly or indirectly encourage IBD related research. In addition, the NIDDK co-sponsored an RFA with NIAID on the use of novel approaches to identify infectious causes of chronic diseases such as Crohn’s disease and ulcerative colitis.

The NIDDK funds multiple applications aimed at understanding the regeneration of the gastrointestinal tract and gastrointestinal immunology. These areas of research are highly relevant to improving the understanding of the fundamental biological problems of intestinal failure and small bowel transplantation. In order to determine the needs of the research community in short gut syndrome, intestinal failure, and small bowel transplantation, a working group meeting is planned to provide recommendations for further research in these important areas.

Item

Interstitial Cystitis – The Committee is aware that there is unprecedented momentum in interstitial cystitis research, particularly in the area of urinary markers. The Committee urges the NIDDK to aggressively support research that will enhance these recent advances. The Committee is pleased that the NIDDK convened a Bladder Research Review Group in 2001 to create a strategic plan and set research priorities for all aspects of bladder disease, including IC. The Committee urges that the strategic plan's recommendations regarding IC be implemented and fully funded as soon as possible. The Committee is pleased with the progress of the IC Clinical Trials group and it urges the NIDDK to re-compete the trials at the end of the current grant period. Since patients with IC frequently get multiple disorders, the Committee also encourages the NIDDK to support collaborative research on IC that includes urologists, neurologists, geneticists, and specialists in visceral pain, vulvodynia, irritable bowel syndrome, and irritable bowel disease. (p. 133)

Action Taken or to be Taken

Please refer to pages 45 & 46 of this document (House item: “Interstitial Cystitis”) for NIDDK’s response to this significant item regarding “Interstitial Cystitis.”

Item

Irritable Bowel Syndrome – The Committee remains concerned about the increasing frequency of irritable bowel syndrome (IBS), a chronic complex of disorders that malign the digestive system. The Committee encourages NIDDK to provide adequate funding for irritable bowel syndrome/functional bowel disorders research and to give priority consideration to funding IBS education/scientific symposiums. Moreover, the Committee urges NIDDK to work with CDC and the private sector to initiate an IBS public awareness campaign. (p. 134)

Action Taken or to be Taken

Please refer to pages 41 & 42 of this document (House item: “Digestive Diseases (IBS)”) for NIDDK’s response to this significant item regarding “Irritable Bowel Syndrome.”

Item

Juvenile Diabetes – The Committee wishes to commend NIDDK for its leadership in implementing the juvenile diabetes research funding approved by Congress last year. The Committee hopes that NIDDK’s juvenile diabetes research portfolio will include such areas as vaccine development, the creation of genomics/bioinformatic capability, initiatives to enhance research training for juvenile diabetes, and the vigorous pursuit of the most promising scientific opportunities to develop alternative sources of insulin-producing beta cells for therapeutic replacement. (p. 134)

Action Taken or to be Taken

Please refer to pages 39 - 41 of this document (House item: “Diabetes”) for NIDDK’s response to this significant item regarding “Juvenile Diabetes.”

Item

Kidney Disease Clinical Research – It has been brought to the Committee's attention that the lack of a permanent infrastructure for clinical trials to study kidney disease is hampering the translation of basic research discoveries to the bedside. In order to provide an organizational framework, the Committee urges the NIDDK to make resources available to plan the development of a Cooperative Clinical Trials Group Program for Kidney Disease Research. (p. 134)

Action Taken or to be Taken

The NIDDK has funded and continues to fund a wide range of kidney disease clinical trials, including the recently completed African American Study of Kidney Disease and Hypertension (AASK) and the planned Chronic Renal Insufficiency Cohort (CRIC) study. The results of these and other clinical trials are expected to greatly advance efforts to prevent the progression of kidney disease, which can lead to renal failure and death. Such trials are invaluable for translating basic and clinical research discoveries into useful therapeutic or preventative approaches for patients with kidney disease. In light of the importance of these trials, the NIDDK has made specific plans to establish a Task Force that can evaluate the development of a Cooperative Clinical Trials Group Program for Kidney Disease Research. A Task Force meeting is planned for March 2002, at which experts will be asked to advise on the issues that might cost-effectively be addressed by a Clinical Trials Cooperative approach, and other strategies to strengthen the infrastructure to perform clinical trials in patients with renal disease. The report that comes from this panel will be used to formulate future initiatives in this area.

Item

Liver Transplantation – The Committee is aware of the significant and continuing shortage of livers available for transplantation, and therefore urges additional research that would facilitate the success of liver transplantation and the number of livers available for transplantation. Many believe that the use of living liver donors may be one of the most important surgical and scientific breakthroughs that can assist people in the need of liver transplants.(p. 134)

Action Taken or to be Taken

Over the last 20 years, liver transplantation has become the standard of care and the only cure for end-stage liver disease. Its success has led to over 4,000 transplants performed yearly; however, at least 17,000 patients are on the transplantation list awaiting cadaveric liver donation. As the waiting list and waiting time have grown, patient mortality has increased while awaiting transplantation and patients are often critically ill by the time of transplantation.

Among possible remedies to the shortage of available organs, living donor liver transplantation (LDLT) has become widely accepted for pediatric transplantation. Adult-to-adult LDLT is a more challenging procedure and of potentially greater risk to the donor because of the larger portion of liver that must be transplanted. LDLT avoids the lengthening waiting period for a donor organ, greatly reduces the ischemic period of the transplanted organ, allows more time for evaluation of the donor, and changes the operation from an emergency into a scheduled procedure. However, LDLT is a difficult and potentially fatal procedure for the donor and provides the recipient with a smaller portion of liver than would have been received through cadaveric transplantation.

To address these issues, NIDDK, in collaboration with NIAID, the Association for the Study of Liver Diseases, and the American Society of Transplant Surgeons, sponsored a workshop on LDLT in December 2000. Subsequently, a Request for Applications (RFA) was issued in July

2001 to invite cooperative agreement applications for clinical and coordinating centers to conduct a Living Donor Liver Transplantation Cohort Study. The objective of this RFA is to establish and maintain the infrastructure required to accrue and follow sufficient numbers of patients being considered for and undergoing LDLT to provide generally applicable data from adequately powered studies. One Data Coordinating Center and as many as eight Transplantation Centers are expected to be chosen through this RFA to participate in planning and implementing a multi-center cohort study on LDLT. Research from this study will provide information to physicians, patients, and potential donors, which they can use to make informed decisions regarding whether LDLT is an appropriate and preferable alternative to cadaveric liver transplantation.

Item

Mucopolysaccharidosis (MPS) – The Committee encourages the NIDDK to expand research efforts in the development of effective treatments for MPS disorders. The Committee encourages the Institute to pursue research addressing genotype-phenotype studies, the blood brain barrier, cell biology, pathophysiology of brain damage and substrate deprivation as they relate to MPS disorders. The Committee urges the NIDDK, NINDS, and NICHD to engage in collaborative research efforts and enhance grant support for current studies as well as new efforts to develop effective therapies for these deadly disorders. (p. 134)

Action Taken or to be Taken

Please refer to pages 49 & 50 of this document (House item: “Mucopolysaccharidosis”) for NIDDK’s response to this significant item regarding “Mucopolysaccharidosis.”

Item

Neurological Disorder-Associated Bladder Dysfunction – The Committee encourages NIDDK to increase funding into the effective treatment of bladder dysfunction associated with spinal cord injury and neurological diseases. The Committee urges NIDDK to investigate the most effective methods of treatment and new and innovative approaches to treatment. (p. 134)

Action Taken or to be Taken

The NIDDK has established a Bladder Research Progress Review Group (PRG) that is serving as a task force for a major strategic review of current NIDDK programs in bladder research. Prominent members of the scientific, medical, and advocacy communities comprise the PRG. The PRG also is articulating a research agenda for the future for bladder research at the NIDDK and NIH. The PRG has met twice and is developing a report on its findings and recommendations. The report will include a review of neurological disorders associated with bladder dysfunction, as well as the biology of innervation of the urethra and bladder. The NIDDK will confer with the NINDS as that chapter develops to review both how these issues have been addressed through current NIH support and how research in this area may be strengthened.

Item

Non-alcoholic Steatohepatitis – Non-alcoholic steatohepatitis liver disease (NASH) is the second-most common cause of liver disease after hepatitis C. The disease is often unrecognized and undiagnosed, and it leads to cirrhosis and liver failure. The Committee urges the Institute to initiate a long-term epidemiological study including research focused on treatment options and outcomes for NASH. (pp. 134-135)

Action Taken or to be Taken

The NIDDK issued a Request for Applications in February 2001, seeking the design and implementation of a database and clinical research network to study the etiology, contributing factors, natural history, complications, and therapy of non-alcoholic steatohepatitis (NASH). Six clinical centers and a data-coordinating center will comprise the NASH Clinical Research Network. Initially, the focus will be on developing a clinical database of patients with NASH and on devising common definitions, nomenclature, and terms for the clinical diagnosis and staging of NASH. The Institute intends that the NASH Clinical Network will provide the preliminary data and background for further investigator-initiated research, and is expected to interact with basic and laboratory research investigators with interest in these diseases by providing reagents, specimens, or opportunities to assess hypotheses on the pathogenesis, prevention, or treatment of the disease. In addition, the Clinical Research Network will establish pilot studies of promising therapeutic approaches and, when appropriate, full-scale clinical trials of therapies for NASH.

Item

Obesity – Obesity is a major health threat in the United States, with more than 49 million American adults considered clinically obese. The Committee urges the NIDDK to expand research in this area, particularly into the effects of obesity on gene expression, as well as excessive risk of gastrointestinal cancers, including colon cancer and liver disease. The Committee also encourages NIDDK to support research in the role of GI hormones, motility, and mucosal absorption in the complex balances of satiety, nutrient uptake and calorie and energy balance. Finally, the Committee urges NIDDK to support research into the effect of diet and nutrient intake on metabolism and gene function to provide further insight into how nutrients conversely affect gut function. (p. 135)

Action Taken or to be Taken

Obesity, the most common nutritional disorder in the United States, is increasing at an alarming rate both in adults and children. The NIDDK has supported research into genetic factors predisposing individuals to obesity and the mechanisms that are affected by these factors, as well as environmental factors contributing to obesity. The Institute currently has active grant portfolios in gastrointestinal (GI) neuroendocrinology and GI transport and absorption that address GI hormonal influence on satiety, hunger, and digestion. Additional projects focus on

neural control of GI functions and the investigation of mechanisms involved in processing macronutrients and micronutrients. The Institute also supports numerous grants investigating nutrient-gene interactions that focus on the influence nutrients have on gene regulation and expression in cells of the GI tract and other organ systems. This research will provide insights that may shed light on a variety of diseases, including gastrointestinal cancers. Studies of hepatic mechanisms in control of food intake and grants exploring the role of the GI tract and gut hormones in the control of energy balance also are supported.

An initiative on clinical studies in bariatric surgery is being developed for FY 2003. A small working group, planned for May 2002, will bring together investigators with expertise in gastrointestinal physiology, neuroendocrinology, behavior, appetite regulation, and energy balance. One of the goals of this working group will be to explore ways in which a surgical model might elucidate the interactions of gastrointestinal factors, motility, and gut-brain signaling and their impact on energy regulation.

NASH is the primary liver disease associated with obesity. The NIDDK is establishing a NASH Clinical Research Network consisting of six clinical centers and a data-coordinating center. The network will focus on the etiology, contributing factors, natural history, complications, and therapy of NASH. This initiative will be funded in FY 2002. Also, NIDDK is supporting an ancillary study to the Look AHEAD (Action For Health in Diabetes) multi-center clinical trial to evaluate the impact of weight loss on NASH in obese patients with type 2 diabetes.

Item

Osteoporosis and Related Bone Disorders – The Committee urges NIDDK to enhance research on osteoporosis, primary hyperparathyroidism and other disorders of calcium metabolism, including renal osteodystrophy, a disorder affecting individuals suffering from chronic kidney disease. NIDDK is also encouraged to enhance its efforts in the areas of nutritional and hormonal influences on calcium and skeletal status and functional genomics in bone. The Committee urges NIDDK to work with NCI to focus on cancer that spreads to bone. (p. 135)

Action Taken or to be Taken

As a result of research funded by the NIDDK in both its extramural and intramural programs, considerable progress has been made in understanding the roles of hormones, growth factors, and cytokines in the regulation of bone. Hormones are major regulators of bone mass and changes in hormone levels may lead to bone diseases. New developments in understanding hormonal mechanisms underlying the regulation of bone formation, on the one hand, and bone loss, on the other, make it possible to develop new therapeutic agents to properly regulate bone turnover and to potentially rebuild bone. This research has potential applicability to a wide range of diseases in which the NIDDK and other NIH Institutes share a mutual research interest. Parathyroid hormone (PTH) is essential to maintaining a proper balance of minerals between bone and blood and can directly stimulate bone growth. Two NIDDK-supported small-scale clinical trials testing the effectiveness of PTH for the treatment of osteoporosis demonstrated that this agent can have a beneficial effect on bone mass. This work has been significantly expanded through industry-supported studies and an FDA advisory committee recently recommended approval of PTH as a

new treatment for osteoporosis. Another promising avenue of research to develop new therapeutic agents of bone disease involves Selective Estrogen Receptor Modulators (SERMS), which can slow, or even stop, further bone loss in patients with osteoporosis.

The NIDDK has supported several important clinical studies addressing research questions identified at a 1990 NIDDK-sponsored NIH Consensus Development Conference, which deliberated how best to treat patients whose very mild, often asymptomatic form of primary hyperparathyroidism could be detected with the advent of a routine measurement of blood calcium. In light of new information generated by recent studies, it is now appropriate to revisit many of these issues. Thus, the NIDDK has scheduled a “Workshop on Asymptomatic Primary Hyperparathyroidism: A Perspective for the 21st century,” for April 8-9, 2002. This workshop is designed to define the current state-of-the-art treatment and generate a research agenda for the 21st century.

Renal osteodystrophy refers to a weakening of the bones caused by poorly working kidneys. It is a common problem for people on dialysis who have high phosphate levels or insufficient vitamin D supplementation. Renal osteodystrophy affects nearly all children with chronic renal failure, and growth retardation is a major clinical consequence. The NIDDK supports a number of research projects on the regulation of bone formation in renal failure and to address the problem of renal osteodystrophy. It is hoped that results from these studies will provide new information on the pathophysiology of renal bone disease and will aid in the development of effective strategies for prevention. The NIDDK also publishes a pamphlet for renal patients and their families on how to “Eat Right To Feel Right on Hemodialysis.” This educational brochure explains how high levels of phosphorous in the blood lead to loss of calcium from bones, making them weak and likely to break, and how the body uses vitamin D to help absorb calcium. The brochure also explains how consumption of other foods affects dialysis and offers suggestions on how to choose the right foods to feel good, including specific information on phosphorous and vitamin supplements.

Item

Parity for Kidney Research – The Committee is concerned that the resources available to conduct kidney research are not keeping pace with inflation. The Committee urges the NIDDK to review the current funding policy and provide increased funding for kidney disease research. (p. 135)

Action Taken or to be Taken

Research into kidney diseases has been and will remain a priority for NIDDK. From FY 1996 through FY 2000, NIH support for kidney research increased from just under \$191 million to over \$277 million. Within NIDDK kidney research funding increased from more than \$119 million in FY 1996 to nearly \$189 million in FY 2000. It is estimated that, in FY 2001, NIDDK will fund \$216 million of kidney research and that the NIH as whole will spend over \$315 million. From FY 1996 through FY 2001, it is estimated that NIH’s funding for research into kidney diseases increased 45 percent and NIDDK’s support increased nearly 60 percent.

Item

Pediatric Kidney Disease – The Committee remains concerned over the alarming number of children and adolescents suffering from kidney disease, a disproportionate number of whom are minorities. In calling for greater research emphasis on this vulnerable segment of our population, the Committee notes that chronic kidney failure among young people results in particularly severe consequences. Normal growth and development are impaired, and many scientists believe that chronic kidney failure has a profound effect on the developing brain, often resulting in learning disabilities and mental retardation. The Committee urges NIDDK to sharpen its research focus on both congenital and acquired chronic renal failure, including: the molecular mechanisms underlying growth failure in children with kidney failure; hypertension as a risk factor for cardiovascular and renal disease; and the development of a database of genetic renal diseases. Additionally, NIDDK is encouraged to launch new training initiatives to help ease the workforce shortage in this field. (p. 135)

Action Taken or to be Taken

Please refer to pages 50 & 51 of this document (House item: “Pediatric Kidney Disease”) for NIDDK’s response to this significant item regarding “Pediatric Kidney Disease.”

Item

Pediatric Liver Disease – The Committee is aware of the “Pediatric Liver Research Agenda 2000: A Blueprint for the Future” developed by the Children’s Liver Council of the American Liver Foundation, which defines research priorities for biliary atresia. Although rare, biliary atresia is the most common cause of liver transplantation in children. Since too few patients are seen annually at individual centers, a collaborative network of centers is needed to gather sufficient data and study specific hypotheses of the cause and treatment of biliary atresia. The Committee encourages the Institute to establish clinical centers and a data-coordinating center to address the scourge of biliary atresia. (p. 136)

Action Taken or to be Taken

Please refer to page 51 of this document (House item: “Pediatric Liver Disease”) for NIDDK’s response to this significant item regarding “Pediatric Liver Disease.”

Item

Phytotherapy – The Committee is aware of the increasing use of patient self-administered phytotherapy (saw palmetto) to treat benign prostatic hypertrophy. However, there is little information available to clinicians or patients regarding the relative safety and effectiveness of this therapy. The Committee encourages NIDDK to move forward on clinical trials aimed at aiding the public and urologists better understanding whether or not there is a role for phytotherapy in treating benign prostatic hypertrophy. (p. 136)

Action Taken or to be Taken

Phytotherapy and other alternative medicines are widely used approaches to the treatment of symptomatic benign prostatic hypertrophy (BPH). The two major phytotherapies, saw palmetto and *Pygeum africanum*, are very widely used for BPH treatment in the U.S., Europe and Asia. The NIDDK plans to establish a trial network with experts in clinical trials on benign prostatic hypertrophy. The network will design and implement full-scale efficacy studies of one or more herbal agents widely used for treatment of prostatic symptoms. A small pilot trial of saw palmetto, co-funded with the NCCAM, is currently under way.

Item

Polycystic Kidney Disease (PKD) – The Committee is encouraged that the number and significance of research discoveries leading to a treatment and cure for PKD are growing at a rapid pace and that notable breakthroughs are coming from the four P-50 PKD research centers established last year by NIDDK. The Committee is also pleased that the NIDDK is planning an International Scientific Workshop focusing on clinical aspects of PKD and an RFA for a PKD Interventional Trials Network, both in early fiscal year 2002. The Committee recommends that the NIDDK fund and execute the PKD Strategic Plan without delay. (p. 136)

Action Taken or to be Taken

Please refer to pages 51 & 52 of this document (House item: “Polycystic Kidney Disease”) for NIDDK’s response to this significant item regarding “Polycystic Kidney Disease.”

Item

Training programs for physicians - The Committee is aware of the need to encourage physicians who wish to pursue careers in the epidemiology of urologic disease and in the development and conduct of urological clinical trials. The Committee encourages NIDDK to initiate a training program to meet these needs. (p. 136)

Action Taken or to be Taken

The NIDDK's Training and Careers Programs offer research training and career development awards in the clinical and basic sciences for pre and post-doctoral training and career development. In addition, the NIDDK recognizes the specific need to enhance urology manpower training efforts, and is conferring with the urologic research community to develop ways to encourage and support physician interest in urology research. In September 2002, the Institute is sponsoring a 3 day workshop on research training in clinical investigation and epidemiology in urology. This workshop will focus on building the skills needed for a successful clinical or epidemiology research career in urology and will specifically target the beginning investigator. Through this and other interactions with the urology community, the Institute anticipates that specific initiatives will be implemented to promote improvements in the urology clinical investigation and epidemiology research workforce.

Item

Urinary Incontinence – The Committee urges the NIDDK to significantly enhance its support of urinary incontinence research following the recommendations from the Bladder Progress Review Group. The Committee encourages the NIDDK to elevate its focus on urinary incontinence research by expanding its support to the Urinary Incontinence Treatment Network Initiative by increasing the number of clinical sites. (p.136)

Action Taken or to be Taken

Please refer to page 53 of this document (House item: “Urinary Incontinence”) for NIDDK’s response to this significant item regarding “Urinary Incontinence.”

Item

Urologic Disorders and Diabetes – The Committee is aware of urological complications such as impotence and urinary retention associated with diabetes. The Committee encourages NIDDK to examine these aspects of diabetes and asks that NIDDK provide the Committee with its plan to address this problem. (p. 136)

Action Taken or to be Taken

The NIDDK has assembled an expert committee, including urologists and urogynecologists, which is formulating a new initiative to address urologic complications of diabetes under the aegis of the Institute’s ongoing Epidemiology of Diabetes Interventions and Complications (EDIC) study. EDIC is a follow-on study to the landmark Diabetes Control and Complications Trial (DCCT), which showed that intensive glucose control in patients with type 1 diabetes greatly reduced the risk for developing microvascular complications, including kidney, nerve and eye disease. EDIC has shown that these benefits have endured and even increased over time since the DCCT was completed in 1993. The new initiative will examine urinary tract infections, incontinence, and sexual dysfunction in the EDIC cohort, and possibly in a control population. Through close collaboration among members of EDIC study group, which includes leading diabetes researchers and biostatisticians, and the expert committee, which provides urologic expertise, the study design is nearly finalized. It was recently positively reviewed by the EDIC External Advisory Committee. The NIDDK is also supporting investigation of urologic dysfunction in patients from the Diabetes Prevention Program clinical trial with impaired glucose tolerance or newly acquired type 2 diabetes.

Item

Urological Disorders Affecting Women – The Committee is aware that urological disorders affect millions of women of all ages. Urinary incontinence is a major cause of nursing home admissions for women. The Committee encourages NIDDK to support research targeted to these problems that may substantially prolong the ability of many elderly women to remain in their homes. (p. 136)

Action Taken or to be Taken

The NIDDK supports research on several urological disorders that primarily affect women, including interstitial cystitis, urinary tract infections, and urinary incontinence. The NIDDK, in collaboration with NICHD, is currently supporting research on urinary incontinence through the Urinary Incontinence Treatment Network Initiative. This multi-center consortium of investigators was established with four vanguard Continence Treatment Centers and a single Biostatistical Coordinating Center. The primary objective of the Network is to evaluate the long-term outcomes of the most commonly applied treatments for women with the diagnoses of stress and mixed urinary incontinence. This much-needed assessment will provide both physicians and patients with information necessary to make well-informed decisions about the best treatment options. To increase the number of patients enrolled and to enhance the ethnic and racial diversity of the study population, the NIDDK added five Continence Treatment Centers to the Network in FY 2001. The new awardees will participate in a four-year prospective cohort study of women who have undergone different surgical procedures for urinary incontinence. This study will use protocols developed through the collaborative efforts of the original centers and the NIDDK and NICHD.

In addition to supporting research studies on urinary incontinence, the NIDDK, through its National Kidney and Urologic Diseases Information Clearinghouse, provides “easy-to-read” and culturally-sensitive publications on bladder control targeted to women, including “Bladder Control for Women”; “Exercising Your Pelvic Muscles”; Menopause and Bladder Control”; “Pregnancy, Childbirth, and Bladder Control”; “Talking to Your Health Care Team About Bladder Control”; “Your Body’s Design for Bladder Control”; and “Your Medicines and Bladder Control”. As part of a coordinated information program to reach minority women (African American and Hispanic and Latino American), who are disproportionately affected by urinary incontinence, these publications are being translated into Spanish. Also as part of this program, the NIDDK plans to work with public and private partners representing African Americans and Hispanic and Latino Americans to identify additional information needs of patients, families, and physicians. Through such partnerships and other efforts, the NIDDK hopes to develop and disseminate further culturally-sensitive messages and materials on bladder control that target minority audiences.

Item

Urology Research – The Committee is concerned that the urology research effort is not addressing the large public health impact of urological diseases and conditions. The Committee encourages NIDDK to increase funding for existing programs in urology research at a growth rate similar to that for the overall agency budget. The Committee is also aware of the significant progress made at the George M. O'Brien Kidney and Urology Research Centers of the NIDDK. The Committee urges continued and increased funding for their activities. In addition, the Committee encourages the creation of two new urologic centers, both of which should have a clinical component and a research training component. (pp. 136-137)

Action Taken or to be Taken

The NIDDK is maintaining a strong commitment to programs in urology research. Overall NIDDK funding for urology research increased an average of 14.3 percent per year between FY 1998 and FY 2001. This growth rate is similar to the overall NIDDK budget increases in that time frame.

As part of its commitment to urology research, the NIDDK has recently funded major epidemiology efforts to assess the large public health impact of urologic diseases and conditions, including the epidemiology study, "Urologic Diseases in America." This study will provide a compendium delineating the changes in the epidemiology, health economic impact, and practice patterns for each of the diseases currently included within the scope of practice of the specialty of urology, analyzed retrospectively over a 10 year period.

The NIDDK, with partial support from the NCI, is currently funding five George M. O'Brien Urology Research Centers. These centers are conducting multiple projects to elucidate the underlying causes of abnormal growth or development of the prostate and genitourinary tract. These studies could lead to improved therapies for conditions such as male infertility and prostate cancer. Grants for the George M. O'Brien Kidney and Urology Research Centers will be re-competing in the Spring of 2002, for funding in FY 2003; at that time the NIDDK will seriously consider the Committee's recommendation for funding of additional sites, based upon the scientific merit of applications received.

The NIDDK is also encouraging innovative research proposals in urology through the recent announcement of a "Pilot and Feasibility" program in urology. This program will make awards to initiate projects aimed at opening up new frontiers in urology research.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2001 Amount Authorized	2002 Estimate	2003 Amount Authorized	2003 Budget Estimate 1/
Research and Investigation	Section 301	42§241	Indefinite	\$1,422,760,000	Indefinite	\$1,559,315,000
National Institute of Diabetes and Digestive and Kidney Diseases	Section 417B	42§285	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	48,055,000	b/	49,977,000
Total, Budget Authority				1,470,815,000		1,609,292,000

a/ Funding provided under the Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act, 2002 (P.L. 107-116).

b/ Reauthorizing legislation will be submitted.

1/ Reflects proposed transfer from the National Cancer Institute

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases
Appropriation History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1994	\$677,135,000	\$716,054,000	\$716,054,000	\$716,054,000
1995 <u>2/</u>	731,500,000	726,784,000	728,784,000	727,628,000 <u>3/</u>
Rescission				(679,000)
1996	748,798,000 <u>2/</u>	771,252,000	738,456,000 <u>2/</u>	771,252,000 <u>4/</u>
Rescission				(670,000)
1997	758,847,000 <u>2/</u>	806,542,000	787,473,000 <u>2/</u>	815,607,000 <u>5/</u>
1998	821,164,000 <u>2/</u>	874,337,000	883,321,000	873,860,000
1999	924,702,000 <u>2/</u> , <u>6/</u>	951,203,000	994,218,000	994,218,000
Rescission				(659,000)
2000	1,002,747,000 <u>2/</u>	1,087,455,000	1,130,056,000	1,147,588,000
Rescission				(6,112,000)
2001	1,186,266,000 <u>2/</u>	1,315,530,000	1,318,106,000	1,303,385,000
Rescission				(429,000)
2002	1,457,915,000	1,446,705,000	1,501,476,000	1,466,866,000
Rescission				(453,000)
2003	1,609,292,000			

1/ Reflects enacted supplementals, rescissions and reappropriations.

2/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.

3/ Excludes enacted administrative reductions of \$679,000.

4/ Excludes enacted administrative reductions of \$670,000.

5/ Excludes enacted administrative reductions of \$375,000.

6/ Reflects a decrease of \$2,790,000 for the budget amendment for bioterrorism.

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases
Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2001 Actual	FY 2002 Estimate	FY 2003 Estimate
Office of the Director	71	70	69
Division of Diabetes, Endocrinology and Metabolic Diseases	21	23	23
Division of Digestive Diseases and Nutrition	18	20	20
Division of Kidney, Urologic and Hematologic Diseases	19	20	20
Division of Nutrition Research Coordination	7	8	8
Division of Extramural Activities	60	60	58
Division of Intramural Research	431	444	444
Total, NIDDK	627	645	642
Statutorily-ceiling exempt FTEs not included above Funds to support these FTEs are provided by Cooperative Research and Development			
FISCAL YEAR	Average GM/GS Grade		
1999	10.9		
2000	11.0		
2001	11.0		
2002	11.0		
2003	11.0		

NATIONAL INSTITUTES OF HEALTH

National Institute of Diabetes and Digestive and Kidney Diseases
Detail of Positions

GRADE	FY 2001 Actual	FY 2002 Estimate	FY 2003 Estimate
ES-6	0	0	0
ES-5	0	0	0
ES-4	3	3	3
ES-3	0	0	0
ES-2	0	0	0
ES-1	0	0	0
Subtotal	3	3	3
Total - ES Salary	\$401,100	\$419,952	\$436,749
GM/GS-15	43	44	43
GM/GS-14	60	60	59
GM/GS-13	48	50	50
GS-12	60	60	60
GS-11	48	50	50
GS-10	5	6	6
GS-9	45	46	46
GS-8	43	44	44
GS-7	39	41	41
GS-6	10	11	11
GS-5	4	4	4
GS-4	8	9	9
GS-3	3	3	3
GS-2	0	0	0
GS-1	0	0	0
Subtotal	416	428	426
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	0	0	0
Director Grade	17	17	17
Senior Grade	6	7	7
Full Grade	5	5	5
Senior Assistant Grade	1	1	1
Subtotal	29	30	30
Ungraded	184	188	188
Total permanent positions	427	433	431
Total positions, end of year	647	669	667
Total full-time equivalent (FTE) employment, end of year	627	645	642
Average ES level	ES-4	ES-4	ES-4
Average ES salary	\$133,700	\$139,984	\$145,583
Average GM/GS grade	11.0	11.0	11.0
Average GM/GS salary	\$69,993	\$73,283	\$76,213